Retro-Diels-Alder routes to 4,5-Disubstituted Cyclopentenones

by

Aklilu Asefaw Kidane

Submitted in accordance with the requirements for the degree of

Master of Science

In the subject of

Chemistry

at the

University of Cape Town

March, 2005

Supervisors: Dr. Eugene S. Sickle, Prof. R. Hunter

I declare that 'Retro-Diels-Alder routes to 4,5-Disubstituted Cyclopentenones' is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

Signed by candidate

Signature Removed

Aklilu Asefaw Kidane

Contents:

Abstract

Investigation into the synthesis of 4,5-disubstituted cyclopentenones was conducted in light of recent interest on cyclopentenone prostaglandins (PGs) as a new class of anti-viral and anti-inflammatory agents.

The strategy involved conjugate addition of various organocuprates to tricyclodecadienone derived from dicyclopentadiene and gave 5-*exo*-substituted tricyclodecadienones.

Attempts to alkylate the kinetic lithium, copper and quaternary ammonium enolates generated from 5-*exo*-substituted tricyclodecadienones with alkylhalides were unsuccessful. Even in the presence of strong cation solvating hexamethylphosphoramide (HMPA) (~30% co-solvent), lithium enolates proved inert. However, trapping the magnesium enolate generated from the 1, 4-addition of *n*-butylmagnesium bromide to tricyclodecadienone with aldehydes yielded β-ketols of *syn* and *anti*-relative configuration. Due to their labile nature, the β-ketols were dehydrated to their corresponding stable enones.

Achiral retro-Diels-Alder reactions were first attempted on 5-*exo*-substituted tricyclodecadienones using several Lewis-acid catalysts. 4-Substituted-2-cyclopentenones were isolated in good yield and no double bond rearrangement or decomposition was observed. Similar results were also obtained with the dienones generated from dehydration of β-ketols to give $\alpha\alpha',\beta\beta'$-unsaturated cyclopentadienones in good yield.

The synthesis of enantiomerically pure 4- Substituted cyclopentenones and 4-butyl-5-butylidene-cyclopent-2-enone *via* chiral Lewis-acid catalysed asymmetric retro-Diels-Alder reactions were unsuccessful. Chiral Lewis-acids were prepared *in situ* from selected Lewis-acids and chiral ligands containing the diol functionality namely BINOL and the TADDOLs.

1. Introduction

Prostanoids are the cyclooxygenase (COX) metabolites of arachidonic acid (AA) and include prostaglandins (PG's) and thromboxanes (TXs).[11,12] PG's contain prostanoic acid as the central structural element (Figure 1) and are classified alphabetically from A to J. The letters identify the functional groups of the cyclopentane ring while a three-numerical subscript series shows the number of double bonds in the side chains (series 1:13-*trans* double bond, series 2: 5-*cis* and 13-*trans* double bonds, and series 3: 5-*cis*, 13-*trans*, and 17-*cis* double bonds) (Figure 2).[11,12]

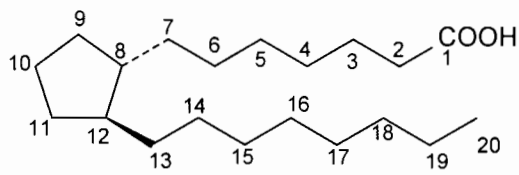


Fig. 1

The PGF family are further subdivided by means of the subscript α and β to distinguish the configuration of the hydroxyl group at position 9.[13] TxA has an oxetane ring instead of the cyclopentane ring.[11]

In eukaryotic cells, arachidonic acid (AA) is liberated from membrane phospholipids in response to various physiological and pathological stimuli. It is consecutively transformed to PGG_2 and PGH_2 with the aid of prostaglandin G/H synthase catalysts known as COX (cyclooxygenase and peroxidase) by addition of molecular oxygen at C-9, C-11 and C-15 positions.[5,11,12] Two forms of COX are recognized. Prostanoids derived from COX-1 are thought to be important in gastric and renal homeostasis. COX-2 on the other hand is rapidly expressed after exposure of cells to hormones, mitogenic stimuli and inflammatory mediators and result in the production of prostanoids that contribute to parturition, inflammation, pain, fever, and certain types of cancer.[12] The ability of aspirin to permanently inactivate both COX isoforms explains its analgesic and anti-inflammatory properties, through COX-2 inhibitions, and its damaging effects on the gastric mucosa, through COX-1 inhibition.[12] PGH_2 is enzymatically processed by discrete PG synthase to

various prostaglandins such as PGD_2 and PGE_1.[11] PGD_2 is a platelet aggregation inhibitory COX product of mast cells and the nervous system,[11] while PGE_1 (Alprostadil) is commonly employed to treat congenital heart disease.[20] PG's of the A and J series are produced by dehydration of PGE and PGD series respectively.[13] Other PG's such as $PGF_{2\alpha}$ reduce the secretion of the progesterone needed for implantation of a fertilised ovum.[14] TxA_2 causes smooth-muscle contraction and also has strong platelet aggregating activity.[12] In addition to the chemically unstable PG's G, H, TxA and I (30s to a few minutes half-life), other stable PG's are metabolised quickly acting only in the vicinity of their production.[8, 11]

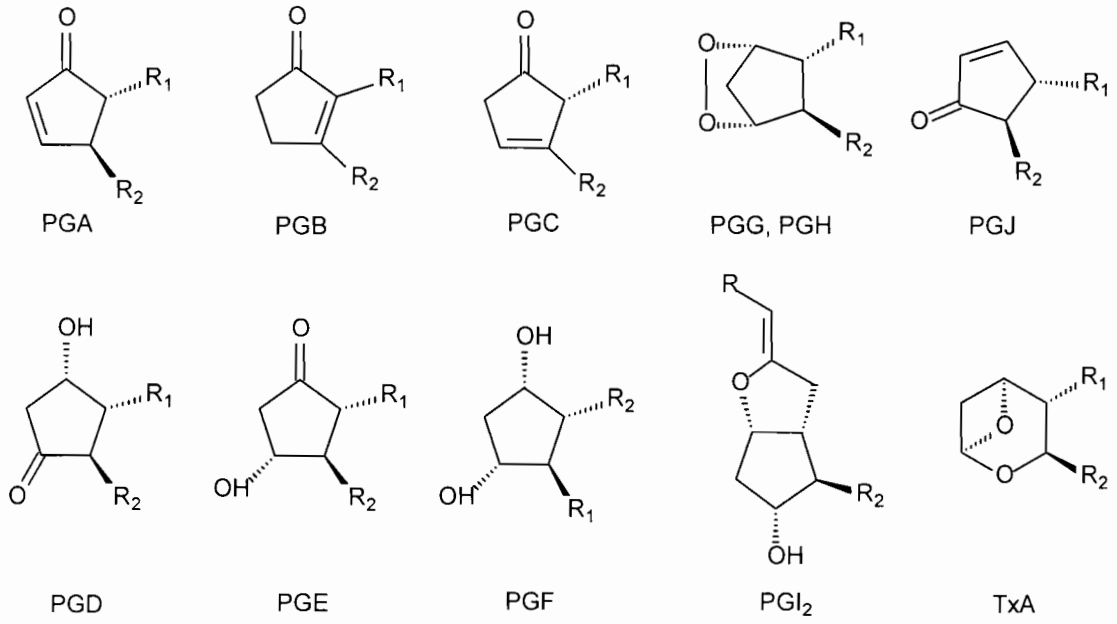
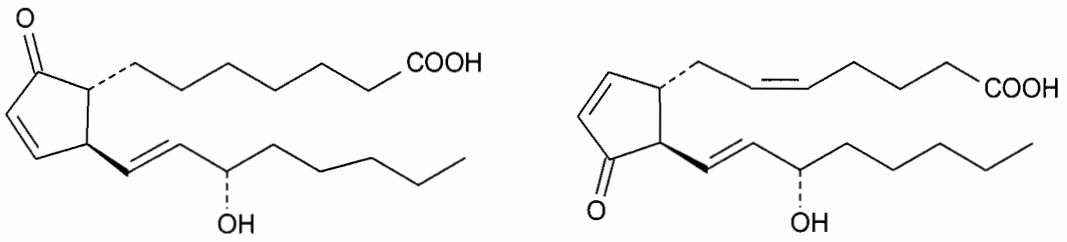


Fig.2 The prostaglandin alphabet

PG_1 series, $R_1=(CH_2)_6CO_2H$; PG_2 series, $R_1=CH_2CH=CH(CH_2)_3CO_2H$, *Z*-alkene, $R_2=CH=CHCH(OH)C_5H_{11}$ (*S*-configuration) except for PG-G when $R_2=CH=CHCH(OOH)C_5H_{11}$

The first antiviral activity of prostaglandins of type A (PGA's), was reported in 1980. Since then there have been numerous reports that PGAs and PGJ's have potent antiviral activity against a wide variety of DNA and RNA viruses in several experimental models *in vitro* and *in vivo* including HIV-1, herpes

viruses, poxviruses, paramyxoviruses, orthomyxoviruses, picornaviruses, togavirusrs and rhabdoviruses.[5,8]



PGA_1 PGJ_2

Fig. 3

Santoro *et al.* have reported more than a 1000-fold reduction in infectious virus yield in HIV-1-infected lymphoblastoid CEM-SS cells when treated with concentrations of PGA_1 and PGJ_2 that do not inhibit nucleic acid synthesis in uninfected cells (Figure 3).[5] Ankel *et al.* also have shown that PGA_1 and PGA_2 dramatically inhibit the replication of HIV-1 in C8166 cells and found the antiviral activity comparable to that of 3'-azido-2'-deoxythymidine (AZT) treatment.[9] The antiviral activity was not due to alterations in the adsorption and penetration of the virus into the cell, nor to an effect on an early event in the HIV-1 replication cycle.[5] Thus, they suggested that HIV-1 RNA transcription could be inhibited in established infections, and recommended a possible use of PGA's or their synthetic analogues as antiviral agents in the treatment of HIV.[5]

A major feature common to antiviral prostaglandins is the ability to function as a signal for the induction of heat-shock protein synthesis.[8] Heat-shock proteins (HSP) are recognized to protect mammalian cells against a wide variety of toxic conditions. These include extreme temperatures, oxidative stress, exposure to heavy metals or cytotoxic drugs, glucose deprivation and virus infection.[1] Their production is not only a signal for recognition of physiological stress, but is utilized by cells in the repair process following different types of injury.[1] Several RNA-viruses induce the synthesis of HSP in host cells during the infectious cycle. Newcastle, sindbis and vesicular stomatitis viruses (in chick embryo cells) and strains of DNA-viruses such as herpes simplex virus (HSV1) and adenovirus in human cells have all been

found to increase the expression of HSP genes.[8] A brief hyperthermic treatment (3 or 4^0C above the physiological range) during specific stages of the virus-cycle is also found to block the replication of several DNA and RNA viruses in cultured cells *via* HSP synthesis.[8] In mammalian cells, several HSP are expressed during normal growth and can be induced by biologically active molecules such as prostaglandins. Others are expressed upon stress-activated regulation of transcriptional and translational switches.[1] Santoro *et al*. have shown that PGA's and PGJ's, that possess antiviral activity against several RNA and DNA-viruses activate the transregulatory heat-shock transcription factor (HSF) protein and induce the synthesis of a major-heat shock and stress-induced 70-κDa HSP (HSP70) in a non-stressful situation in a wide variety of human and mammalian cells.[1,5,8]

Induction requires the activation and translocation to the nucleus of HSF. HSF exists as an inactive non-DNA binding form and rapidly converts to the DNA-binding form upon exposure of the cell to heat shock or other stimuli.[2] In the nucleus, HSF binds to specific heat-shock elements (HSE) which are located upstream of heat shock-genes and activates transcription (e.g. HSP70)[1] (Figure 4). The induction of HSP70 by prostaglandins requires the presence of a reactive α,β-unsaturated carbonyl group in the cyclopentane ring. This group forms Michael's adducts with cellular nucleophiles and covalently binds to cysteine residues of proteins (IKKβ and IKKα) *via* a thioether bond and resulting in HSF activation.[1] The cyclopentenone ring core-structure itself has also been shown by Santoro *et al* to selectively induce the expression of 70-κDa HSP (HSP70), demonstrating the α,β-unsaturated carbonyl group as the key structure triggering HSF activation.[1] However, PGA_1 is able to activate HSF at concentrations much lower than 2-cyclopenten-1-one. The presence of the aliphatic side-chains could be functional by facilitating either entry into cells or detection of binding to the molecular target.[1] The cytoprotective role of heat-shock proteins (HSP) described in a variety of human diseases, including ischaemia, inflammation and infection, suggests new therapeutic strategies relying upon the development of drugs that selectively turn on heat -shock genes.[1,3]

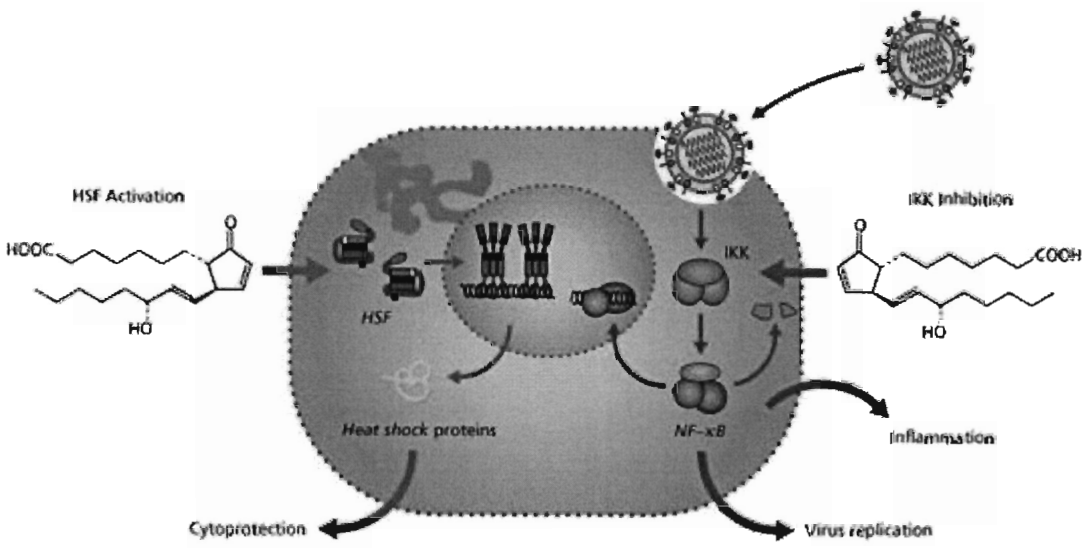


Fig. 4 (Chemistry in Britain, May 2001)[14]

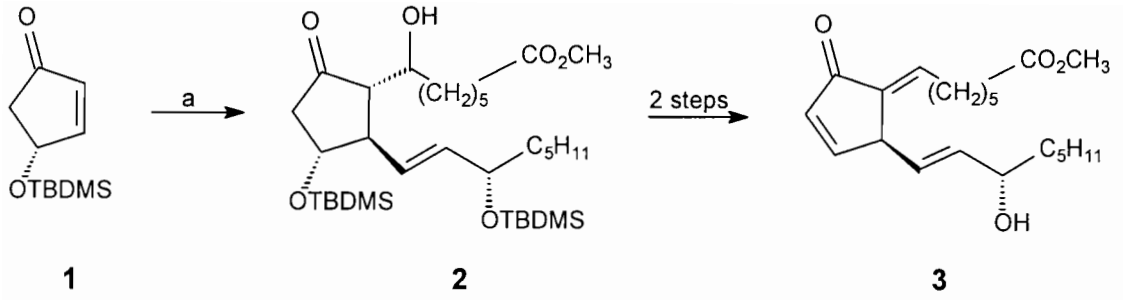
The anti-inflammatory activity and inhibition of HIV-1 RNA-transcription also appears to be mediated by the ability of cycPG's to inhibit the activation of nuclear factor-κB (NF-κB).[4,10] NF-κB is a critical regulator of the immediate, early pathogen response and of the activation of the immune system. It is involved in many pathological events such as the progression of AIDS by enhancing HIV-1 transcription.[9] An inducible transcription factor, NF-κB exists in an inactive cytoplasmic complex bound to inhibitory protein of the IκB (usually IκBα), and is activated in response to pathogenic stimuli. Stimulation triggers phosphorylation by the catalytic IKK complex and degradation of IκBα resulting in NF-κB translocation to the nucleus. In the nucleus, NF-κB binds to DNA at specific κB-sites rapidly inducing a variety of genes encoding signalling proteins (Figure 4).[6,7] Target genes include cyclooxygenase-2 (COX2), nitric-oxide synthase, several inflammatory and chemotactic cytokine receptors, cell adhesion molecules as well as viral genes.[6]

Cyclopentenone PG's act by preventing degradation of IκBα and are dependent on the presence of a reactive cyclopentenonyl moiety.[4] The NF-κB inhibitory effects by cyclopentenone PGs' and other inducers (such as sodium arsenite or hyperthermia) is closely associated with HSF-activation in

humans. This suggests the possibility that triggering HSF1 could render cells unresponsive to NF-κB stimulation.[4] In *in vivo* and *in vitro* models of human cells stimulated by tumour necrosis factor (TNFα), cycPGs of the A and J series have shown to inhibit IKK activity by direct modification of its IKKβ subunit. The presence of an α,β-unsaturated carbonyl group that forms Michael adducts with cellular nucleophiles and covalently modify specific proteins was essential for IKK inhibition.[7] For this reason, the development of novel molecules characterized by the ability to activate HSF while inhibiting NF-κB and being devoid of the pleiotropic effects of natural PG's for therapeutic intervention in inflammatory and infectious diseases is widely recognized. In addition to their wide spectrum of antiviral activity and absence of viral resistance to these drugs, cyclopentenone PGs form an interesting new class of antiviral agents.[14] A large variety of prostanoid analogous to PGA can also be obtained from natural marine organisms.[5,8]

1.1. Cyclopentenone prostaglandin synthesis

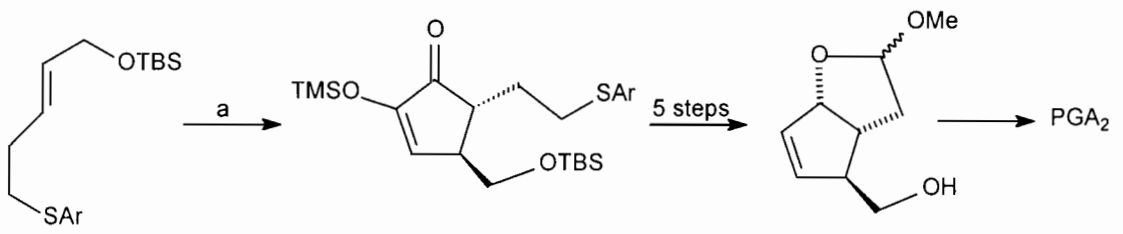
Cyclopentenone PG's began to emerge as an attractive class of prostanoids in the early 1990's. To date, a number of elegant synthetic approaches to these PG's and analogues have appeared in the chemical literature.[20] Noyori's three-component coupling protocol was initially designed to gain efficient access to the PGE's series. It involves simplification with dimethylzinc instead of the combined use of a phosphine-complexed organocuprate and organotin chloride.[20] The clinical candidate Δ^7-PGA_1 methyl ester[2] **3**, used for the treatment of chemotherapy resistant ovarian cancer, is made using this procedure. A functionalised vinyllithium in the presence of Me_2Zn is first attached to **1** *via* a 1,4-addition. A *trans*-electrophilic trapping of the enolate intermediate with methyl-6-formylhexanoate followed by a two-step simple dehydration gives **3**. Added Me_2Zn suppresses the lithium-enolate double bond migration in the presence of proton sources and facilitates direct alkylation (Scheme 1).[15,20]



1 **2** **3**

Scheme 1: a) (*1E*, *3S*)-LiCH=CHCH(OR)C_5H_{11}, $ZnMe_2$, THF, - 78^{0}C then $HCO(CH_2)_5CO_2Me$, -78 to 30 ^{0}C, 97% , R= TBDMS.

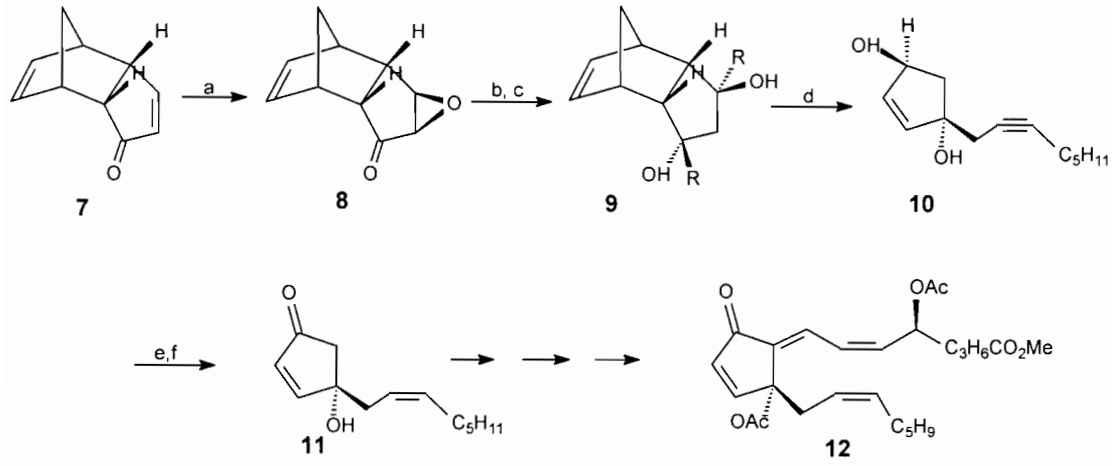
In an alternative PG-synthesis, the sulfide-directing Pauson-Khand cycloaddition of 1,2-disubstituted alkenes has been used by Corey for the synthesis of PGA_2. The key step was the synthesis of acetal **6**, and *trans-4,*5-disubstituted-2-cylopentenone **5** intermediate was obtained in good yield and then transformed into **6** in five steps. (Scheme 2).[19]



4 **5** **6**

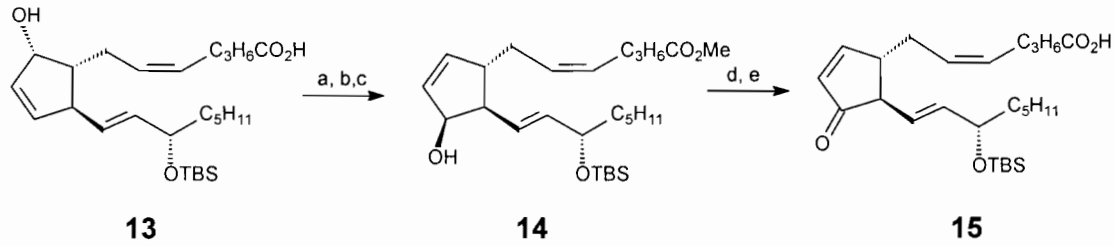
Scheme 2: a) [(trimethylsilyl)acetylene] hexacarbonyldicobalt comp., $PhCH_3$, 95^{0}C, 30 h, 79%

Zwanenburg *et al.* have described an enantio- and stereoselective synthesis of clavulone **12** from the key PG-intermediate γ-hydroxycyclopentenone **11** (Scheme 3).[20] A nucleophilic octynylzinc addition to the carbonyl group of *exo*-epoxy ketone **8** obtained from **7** was followed by reductive opening of the epoxide ring. Subsequent cycloreversion of **9**, selective oxidation of the secondary hydroxyl group and reduction of the side-chain triple bond in **10** led to **11** in six overall steps.



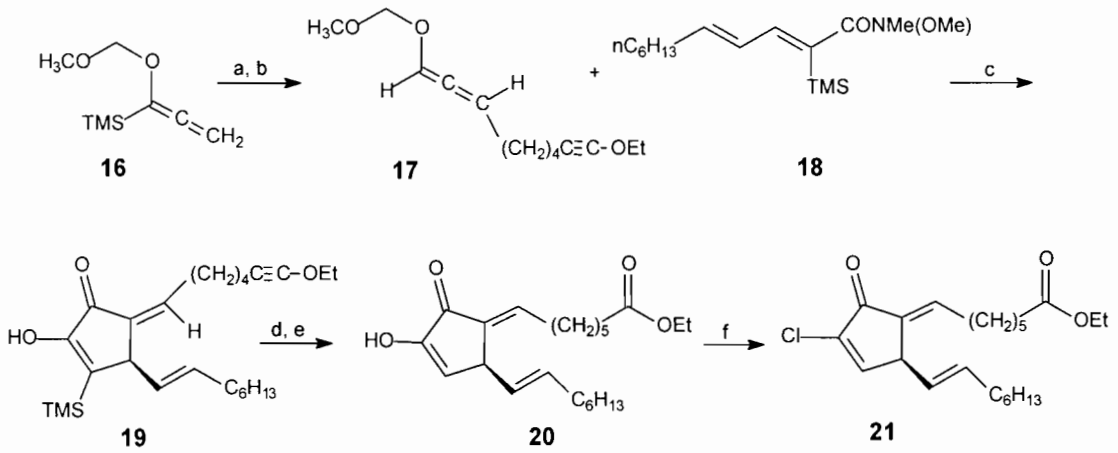
Scheme 3: a) H_2O_2, OH^-, rt, 100%, b) RZnBr, rt, 90%, c) $LiAlH_4$, rt, 3 d, 77%, d) FVT, 500^0C, 10^{-2} mbar, 72%, e) PCC, DCM, 91%, f) H_2, Lindlar cat, toluene.

From the PGJ_2 series, 15-deoxy-$\Delta^{12,14}$-PGJ_2 was found to be the natural activating ligand for peroxisome proliferator-activated receptor gamma (PPARγ), the molecular target of antidiabetic drugs. In spite of this discovery, less attention was given to PGJ_2 synthesis.[17] Recently Giovanni *et al.* reported a general A-J swap method. This method transforms an advanced PGA_2 synthetic intermediate into a suitable synthon for the PGJ_2 series synthesis.[17]The methyl ester of hydroxyl acid **13** (used in Robert's PGA_2 synthesis) was exposed to *o*-nitrophenyl selenocyanate and Bu_3P in THF. Subsequent oxidation of the S_N2 selenide product with 30% H_2O_2/pyridine promoted [2,3] sigmatropic rearrangement of the intermediate allylic selenoxide to give isomeric alcohol **14** (Scheme 4).



Scheme 4: a) CH_2N_2, Et_2O, 0^0C, quant. b) *o*-nitrophenyl selenocyanate, Bu_3P, THF, rt, 78% c) H_2O_2 30%, Py, 7^0C, THF, 55% d) $Ba(OH)_2.8H_2O$, MeOH, rt, 73% e) DMP, DCM, rt, 80%.

Halogenated PG's **21** are more potent than Δ^7-PGA_1 in anti-neoplastic assays both *in vivo* and *in vitro*.[18,20] Marcus A *et al.* addressed a convergent approach to the synthesis of a halogenated Δ^7-PG skeleton by applying a cyclopentannelation strategy.[18] Thus deprotonation of the α-proton of allenic ether **17** (2 equiv.) with *n*-BuLi was followed by reaction with the Weinreb amide **18** (1 equiv.) obtained from 1-butyne in four steps. Work-up of the reaction with aq.NaH_2PO_4 led to a spontaneous cyclization *via* Michael addition to the enone intermediate furnishing **19** in a *Z/E* = 6/1 selectivity. The selectivity is a kinetic preference which can be ascribed to the more favourable conrotation which occurs when the aliphatic chain on the allene rotates away from the lower side chain.[18] Exposure of **19** in moist trichloroacetic acid resulted in hydrolysis of the acetylenic ether, protiodesillylation and isomerization of the exocyclic, conjugated double-bond to furnish **20**. Applying Ponara's chlorination to **20**, the dimethylthiocarbamate was first isolated in 84% yield and then heated in the presences of LiCl to give Δ^7-10-chloro-15-deoxy PGA_1 **21** (Scheme 5).



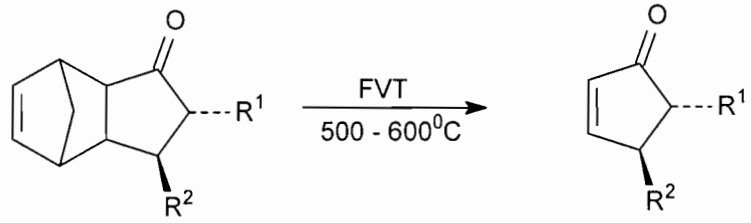
Scheme 5: a) *t*-BuLi, THF, - 78^{0}C, 1,4-dibromobutane, - 40^{0}C to – 20 ^{0}C, 91% b) lithium ethoxyacetylide, liq NH_3, - 78^{0}C, 62% c) *n*-BuLi, THF, - 78 ^{0}C;**18**, THF, - 78^{0}C, aq NaH_2PO_4, 80% d) Cl_3CCO_2H, DCM, H_2O, rt, 55% (from 15) e) dimethylthiocarbamoyl chloride, DABCO, DCM, 0^{0}C, 84% f) H_3CCN, HOAc, LiCl, 80^{0}C, 79%.

The discovery of other antibiotic and/or antitumor cyclopentanoids such as halovulone **21** (Scheme 5), initiated enormous synthetic activity aimed at

developing effective stereo- and enantioselective methods for the construction of highly functionalised cyclopentanoids.[33]

1.2. Rationale of the project

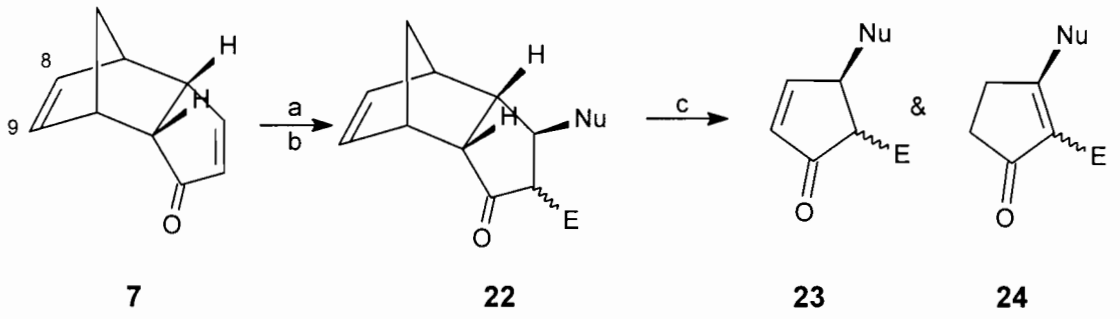
Even though the structure of cyclopentenone PG's appear simplistic, their sensitivity towards acidic or basic media can result in double-bond rearrangement and/or extensive decomposition.[39] This has promoted chemists to include a retro-Diels-Alder thermal cleavage in their synthetic strategy towards these compounds.[68] As a result, retro-Diels-Alder reactions of the type in Scheme 6 have received considerable attention in natural product synthesis. They allow the stereospecific formation or regeneration of an olefin. These reactions are routinely conducted under high temperature (500-600^{0}C) flash vacuum thermolysis (FVT) and permit the preparation of thermodynamically less-stable 4,5-dialkylcyclopent-2-enones rather than the more stable 2,3-dialkylcyclopent-2-enones.[39]



Scheme 6:

Substituted tricyclodecadienone **7** and tricyclodecenone intermediates **22** are currently being used extensively in the synthesis of naturally occurring cyclopentanoids.[40] The strategy followed by Zwanenburg *et al.* and others towards these compounds is illustrated in Scheme 7. In the first two steps, the enolate generated from a diastereoselective nucleophilic β-conjugate addition to enone **7** is trapped with electrophiles at the α-position. Thermal [4+2] cycloreversion of 4,5-disubstituted tricyclodecenones (**22**) gives functionalised cyclopentenones with well-defined relative stereochemistry (**23**).[34] Because of the C_8-C_9 steric hindrance created by the ethylene-bridge in **7** (concave-face), nucleophilic β-attack at this side is severely hindered and addition occurs at

the sterically less-hindered convex face.[28,33,34] The success of this approach depends on the availability of **7** in enantiopure form either by enzymatic[25,27,36,37] or non-enzymatic[26,38] resolution of one of its precursors.



7 **22** **23** **24**

Scheme 7: a) Nucleophilic (Nu^-), b) Electrophile (E^+), c) Lewis acid / Δ

In a related study, norbornene derivatives of type **22** have been reported by Grieco to undergo Lewis-acid catalysed retro-Diels-Alder reactions in the presence of reactive dienophiles. Maleic anhydride and fumaronitrile are commonly used as dienophiles to drive the reaction to completion.[42] In the absence of these dienophiles, **23** (E=H, Nu=Bu^n) was isolated in 10% yield.[42] In contrast to this, Marchand *et al.* reported the synthesis of cyclopentenones (>70%) *via* boron trifluoride etherate ($F_3B.OEt_2$) mediated [4+2] cycloreversion in the absence of added dienophiles.[40] Using Grieco's method, the thermodynamically more-stable rearranged enone **24** (E=H, Nu= Bu^n) was not formed when the relatively simple norbornene derivative **22** (E=H, Nu= Bu^n) was subjected to cycloreversion. In contrast, prolonged exposure of acid/base sensitive natural product 12-oxophytodienoic acid **23** (Nu= $(CH_2)_7CO_2H$, $E=CH_2CHCHC_2H_5$) to acid led to the more stable rearranged isomer **24**.[42]

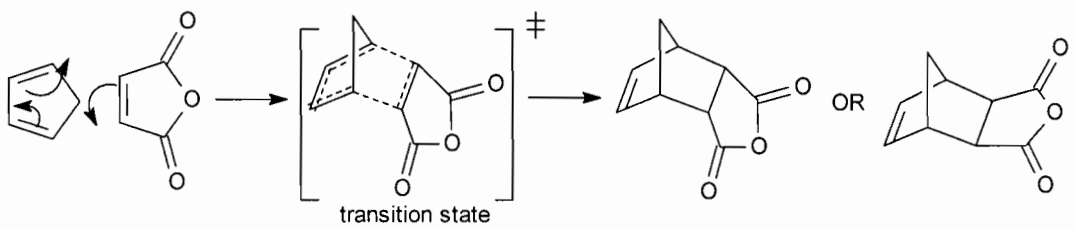
The objective of the first phase of the project was to investigate several aluminium, titanium and boron Lewis-acids in the retro-Diels-Alder reactions of *exo*-5-substituted tricyclodecenones **22** (E=H, Nu=R) depicted in Scheme 7. The amount of catalyst required, temperature and conversion rate of these reactions has been investigated. In the second phase of the project, a novel methodology for generating 4,5-disubstituted cyclopentenones **23** (E=R) in enantiomerically pure form was explored. The aim of the latter part of the study was to ascertain the feasibility of an asymmetric Lewis-acid catalysed

retro-Diels-Alder reaction. Chiral Lewis-acids may be generated by reacting optically pure diols with Lewis-acids identified from the achiral retro-Diels-Alder reactions.

1.3. The Diels-Alder reaction

The Diels-Alder reaction is a one step [4+2] cycloaddition between a conjugated diene and activated alkene (the dienophile). It involves electrons moving out of π-orbitals into σ-orbitals in a concerted fashion and allows the formation of up to four asymmetric centres (Scheme 8). In frontier orbital terms, the reaction involves a combination of the dienophile's low energy LUMO and the diene's high energy HOMO in a stereospecific fashion to produce an adduct with a well-defined relative stereochemistry.[68] The transition-state has 6 delocalised π-electrons and is aromatic in character, having the same stabilization of benzene (Scheme 8).[69] For the reaction to proceed, the diene component must adopt the s-*cis* conformation and the dienophilic π-bond be activated by the presence of electron-withdrawing groups that lower the alkene LUMO (the π^*-orbital of the alkene) and thus increase reaction rate.[69]

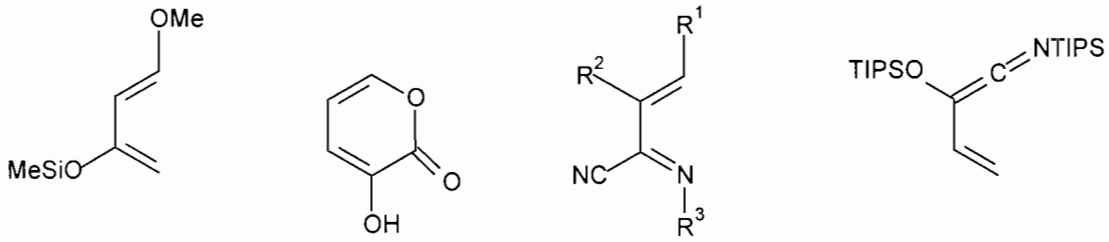
Scheme 8 shows two possible products of different diastereoselectivity. According to the Alder-rule, the *endo*-approach **27** is favoured because it involves better accumulation of double-bonds.[69] The *endo*-selectivity further increases when the energy of the LUMO of the dienophile decreases and the coefficient at the carbon atom containing electron-withdrawing groups increases.[69]



25 **26** **27** **28**

Scheme 8:

The discovery of practical methods of preparation of highly functionalised dienes has played a significant role in making the Diels-Alder reaction a versatile tool. Exemplified in Figure 5 are some representative examples of such dienes (Figure 5).[68]



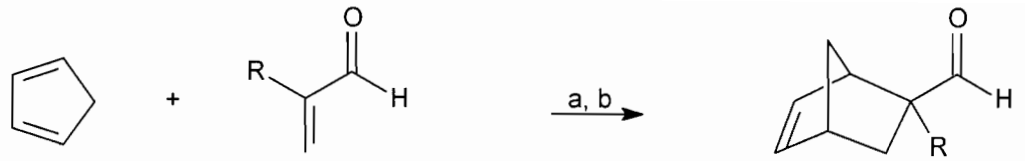
Danishefsky | Corey | Fowler Grierson | Ghosez

Fig. 5

The electro-withdrawing capacity and electrophilic reactivity of dienophiles can be enhanced by addition of Lewis acids which form complexes with polar substituents of the dienophiles.[63] A significant lowering of the LUMO energy of the dienophile is responsible for the acceleration and enhanced selectivity usually observed in a HOMO (diene)-LUMO (dienophile) controlled step.[64]

1.3.1. Catalytic Asymmetric Diels-Alder Reactions

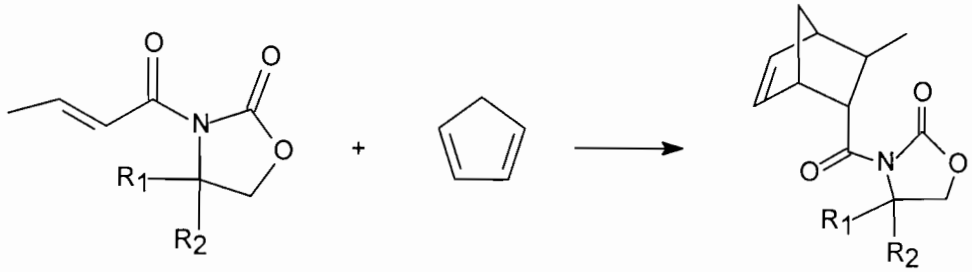
Catalytic asymmetric Diels-Alder reactions are the subject of intense research for creating six-membered carbo- and hetrocyclic compounds in a regio-, diastereo- and enantiocontrolled way.[67,68] A small amount of expensive chiral material is required and the final product obtained directly. The chiral catalysts are a modification of Lewis-acids that have been successfully used in the Diels-Alder reaction (based mainly on boron, aluminium, or titanium).[65] Koga *et al* published the first significant result in 1979 for the cycloaddition of methacrolein **29a** and cyclopentadiene **25** catalyzed by menthyloxydichloroaluminum prepared *in situ* from (-) menthol and ethylaluminum dichloride (Scheme 9).[65]



25 **29a, 29b** **30a, 30b**

Scheme 9: a) 0.15 mole equiv. [mentOAlCl$_2$], PhCH$_3$, - 78^{0}C, **30a** (R = Me), 69%, 64% *ee* exo, b) 5 mol % of **43**, - 78^{0}C, 1h, **30b** (R = Br), 95%, 99.5% *ee*, 96% exo.

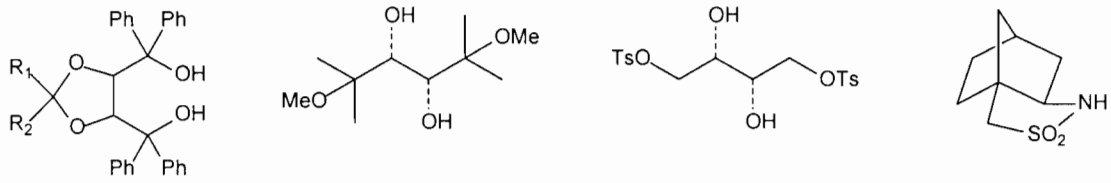
Chiral titanium reagents are prepared *in situ* by azeotropic removal of isopropyl alcohol from chlorotitanium isopropoxides and chiral diols. Seebach *et al.* reported the condensation of methyl acrylate and cyclopentadiene to give the *endo* adduct in 42-50% *ee* when binol was introduced on titanium.[67] Similarly, Narasaka *et al.* reported the use of a chiral titanium reagent (2 mole equiv.) which was azeotropically generated from a tartrate-derived 1,4-diol and dichlorotitanium diisopropoxide (TiCl$_2$(OPr-*i*)$_2$) to promote the Diels-Alder reaction of *N*-crotonoyl-1,3-oxazolidin-2-one **31a** and cyclopentadiene to give **32a** as the major *endo*-adduct (91% *ee*) (Scheme 10).[30] In the presence of 4A MS, the same reaction at 0^{0}C gave a comparable *ee* on using catalytic (10% mole equiv.) amount of the reagent. From NMR studies, the beneficial effect of the molecular sieves appeared to be to shift the equilibrium towards the formation of the chiral complex.[65,67]



Scheme 10: **31a** R_1=R_2=H **32a** R_1=R_2=H
33b R_1=R_2=Me **34b** R_1=R_2=Me

In a study by Chapuis *et al.*, chiral aluminum chlorides generated *in situ* from ethylaluminum dichloride (EtAlCl$_2$) and chiral diols **35**, **36**, **37** and sulfonamide **38** (Figure 6) were stoichiometrically utilized at - 78^{0}C in forming the Diels-

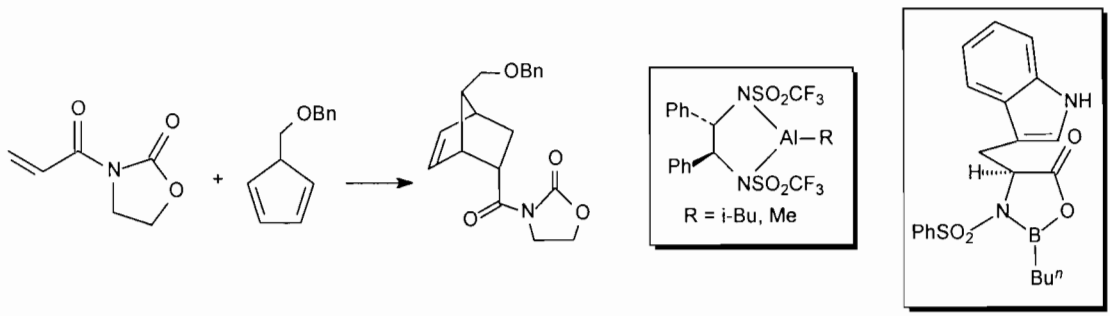
Alder adduct **34b** in high optical purity (92-98%).[67] However, use of these chiral complexes is limited only to the bidentate crotonate dienophile **33b** as the *ee* drops when an acrylate analogue is used as a dienophile (Scheme 10).[67]



35 **36** **37** **38**

Fig. 6

Corey *et al.* have developed chiral aluminium complexes **42** derived from chiral bis-sulphonamides having C_2-symmetry. Using **42**, a synthetic intermediate prostaglandin **41** has been prepared with 95% optical purity (Scheme 11).[65] At the time of its publication, the highest *ee* reported was by Corey *et al.* who used (*S*)-trytophan-derived oxazaborolidine **43** as a catalyst in the cycloaddition of cyclopentadiene **25** and 2-bromoacrolein **29b**. Using 5 mole % of **43**, bromoaldehyde **30b** was obtained in 99.5% *ee* (Scheme 9).[66]



39 **40** **41** **42** **43**

Scheme 11:

1.4. Retro-Diels-Alder reactions

With the introduction of flash vacuum thermolysis (F.V.T), retro-Diels-Alder reactions can now be extensively applied in the synthesis of a wide variety of natural products.[42] The search for retro-Diels-Alder reactions operating at lower temperature using selected dienes has allowed the synthesis of complex and labile natural products.[41] Representative examples of these natural products featuring cycloreversion as the key step are presented below in Figure 7.[41]

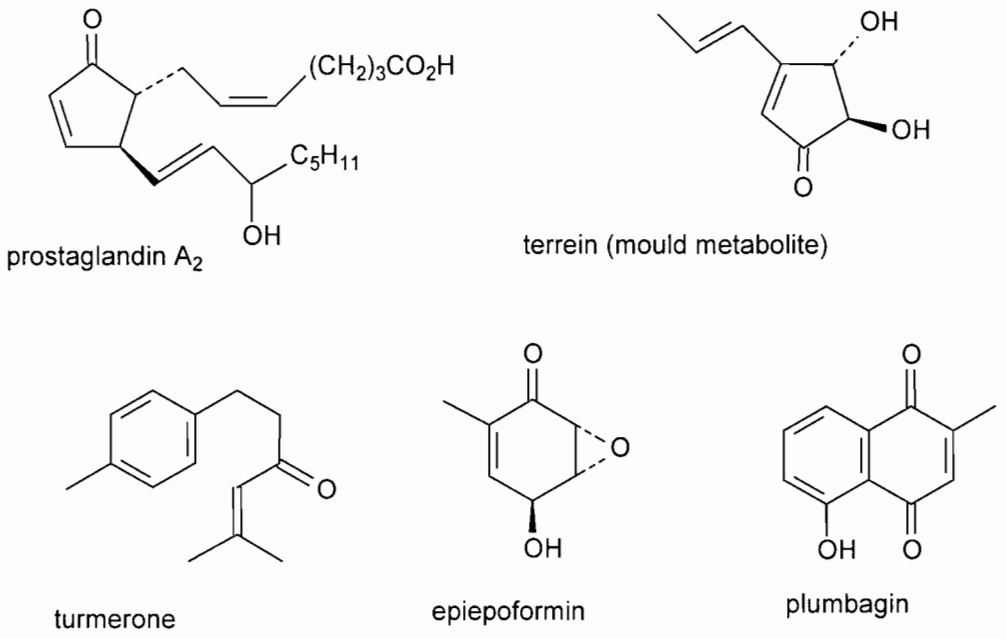
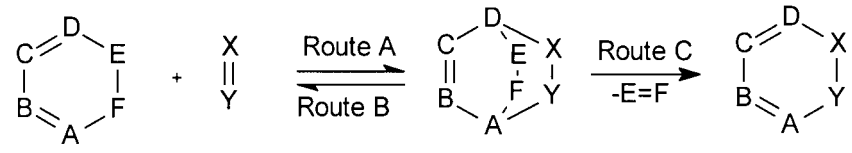


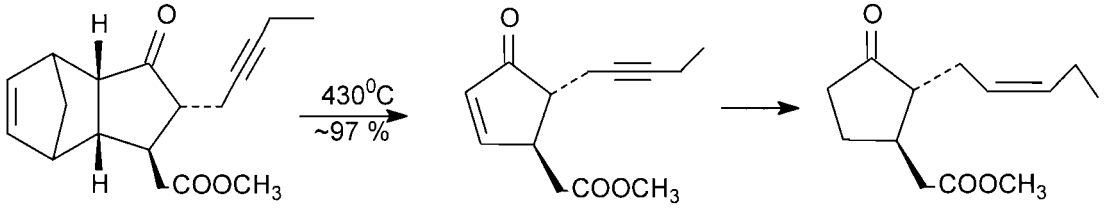
Fig. 7

Retro-Diels-Alder reactions can undergo two different fragmentations (Scheme 12).[41] One of these is the regeneration of the starting moieties (Route B), and is useful for protection during modification of the diene or the dienophile fragment. The second fragmentation pattern (Route C) is followed only when its activation energy is lower than that of Route B. This situation generally occurs if the dienophile (E = F) is a very stable molecule such as acetylene, ethylene, carbon dioxide, nitrogen or nitriles.



Scheme 12:

Dicyclopentadiene has been a convenient source for the synthesis of cyclopentanoid natural products through cycloreversion of its derivatives. Methyl jasmonate **46** was prepared from cyclopentenone **45** obtained *via* thermolysis of the pentanone derivative **44** with the side chains appropriate to the target (Scheme 13).[41]

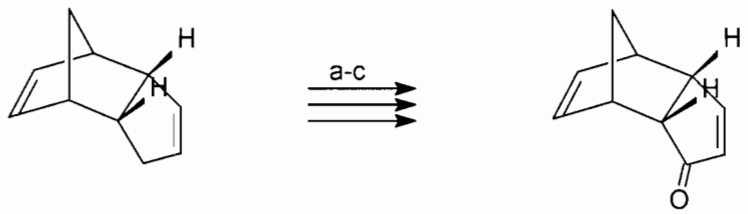


44 **45** **46**

Scheme 13:

1.5. Synthesis of starting material

Starting material (**7**) was envisaged as being available in three steps starting from dicyclopentadiene **47** (Scheme 14). The first step involves the use of a one-step allylic oxidation of the five-membered ring to afford the allylic acetate.[24] Hydrolysis of the acetate furnishes the corresponding alcohol which is subsequently oxidized to **7**.



47 **7**

Scheme 14: a) $Mn(OAc)_3$/KBr (cat.), AcOH, b) K_2CO_3/ MeOH, c) PCC/Alumina.

The potential of **7** as a synthon for cyclopentanoid synthesis lies in its rigid tricyclic structure.[36] Being a Diels-Alder adduct of cyclopentadiene and cyclopentadienone in which one of the double bonds of cyclopentadienone is masked, chemical transformations at the remaining enone functional group are stereoselective.[34,37] Cycloreversion of the substituted **7** under FVT or Lewis-acid conditions generates the unmasked enone functionality hence furnishings functionalized cyclopentenone intermediates with well-defined stereochemistry.[33,36,37] Consequently, there is enormous interest in the use of substituted tricyclic **7** for the construction of a large variety of biologically active natural products containing five-membered rings (cyclopentanoids).[40] Hence using the tricyclic system of **7**, we aimed at developing an effective stereo- and enantio-selective method towards simple analogues of functionalized cyclopentenones (Scheme 7).

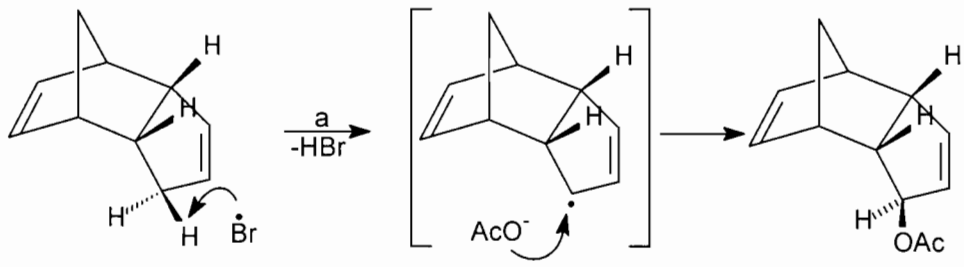
2. Results and Discussion

2.1. Synthesis of starting materials

Exo-3-Hydroxydicyclopentadiene **49** and its acetate **48** serve as suitable precursors for dicyclopentadienone **7**. Enone **7** has been used in the enantio- and stereo-controlled synthesis of a variety of cyclopentanoids.[24,28] The most convenient route to **48** and **49** is selenium dioxide oxidation[24,27] of dicyclopentadiene **47**, which permits introduction of the oxygen functionality at the required allylic-position. However, the toxicity of selenium dioxide reagents led Ogasawara and co-workers to explore alternative procedures and they have reported a one-step preparation of acetate **48** from dicyclopentadiene (Scheme 16).[24] Their procedure involves treatment of dicyclopentadiene with manganese (III) acetate, prepared *in situ*, in a warm mixture of acetic acid and acetic anhydride in the presence of potassium bromide to generate **48** in a stereospecific manner. The role of acetic acid-acetic anhydride solvent system is to increase the rate and yield of the reaction and the solubility of $Mn(OAc)_3$.[23] Using this procedure on a 36 mmol scale preparation, the acetate was obtained in reasonable yield (70%) after purification by column chromatography. The large-scale preparation (~150 mmol) of this material suffers from reduced yield and longer reaction time (~40%, >3 h). The yield of this procedure is comparable with that of the selenium dioxide procedure which gave 3-hydroxydicyclopentadiene **49** in 57%.[24] Spectral data were identical with those of authentic material and showed diagnostic acetate group ^1H NMR and ^{13}C NMR resonances (3 proton *s* at δ_H = 2.01 ppm and carbon at δ_c = 171.00 ppm) and an IR peak at 1720 cm^{-1}.

The oxidant ($Mn(OAc)_3.2H_2O$) was synthesized from $Mn(OAc)_2.4H_2O$ and $KMnO_4$ in order to provide a $Mn(OAc)_3$ of consistent quality. The transfer of an electron from bromide ion to the one-electron oxidant manganese (III) is thought to produce a bromine radical which may co-ordinate to the reduced oxidant. The resulting species abstracts a hydrogen atom from the allylic position of the olefin to form an allylic radical intermediate which is

subsequently intercepted to give an allylic acetate and an allylic bromide.[21,22] Under the given reaction conditions, the allylic bromide is further converted to the allylic acetate.[22] In this reaction the role of potassium bromide is to accelerate the rate of oxidation of **47** to the corresponding allylic acetate **48**.[24] In a related work, the oxidation rate of toluene to benzyl acetate by manganese (III) acetate has also been reported to increase in the presence of metal halides.[22] The *exo*-approach of the acetate group is rationalised from the structure of **47** which limits approach to the sterically congested concave face, favouring approach of the acetate to the convex face. The *cis*-stereochemistry of protons H-2 and H-6 was confirmed from their coupling constant (~ J = 9.5 Hz, $CDCl_3$). This coupling constant is consistent with the angle between H-2 and H-6 deduced from molecular models.[31] Scheme 15 illustrates a possible reaction pathway for the synthesis of acetate **48** from dicyclopentadiene **47**.



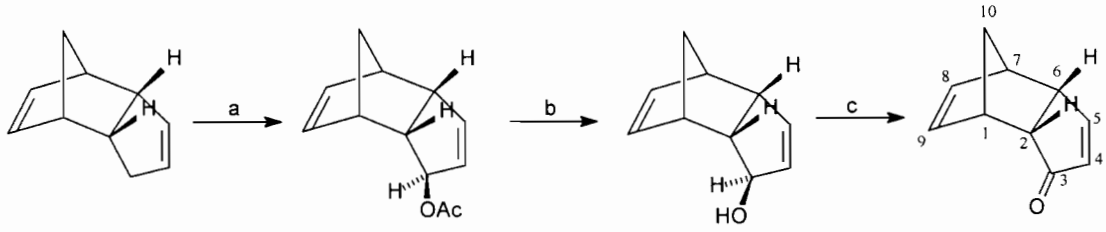
47 **48**

Scheme 15: a) $Mn(OAc)_3$, $KMnO_4$, KBr (cat.), AcOH, Ac_2O, 70^{0}C, 1 h

Exo-3-hydroxydicyclopentadiene **49** was prepared by hydrolysis of *exo*-3-acetoxydicyclopentadiene **48** with K_2CO_3 in methanol for 20 h. After work-up, the crude material was chromatographed on silica to give a colourless crystalline *exo*-alcohol in 90% yield (Scheme 18). The disappearance of the acetate singlet (δ_H = 2.01 ppm) and carbonyl (δ_C = 172 ppm) peaks and appearance of a weak broad singlet for the OH proton (δ_H = 1.47 ppm) confirmed the hydrolysis of the acetate. In addition, a characteristic IR O-H stretching frequency of 3682 cm^{-1} and mass spectra confirmed the formation

of **49**. Melting point and spectroscopic data were also in agreement with literature values.[24]

The next synthetic step required oxidation of **49** to enone **7**. This was achieved after 12 h stirring of **49** in hexane with pyridinium chlorochromate on alumina (PCC/Alumina). The oxidant was prepared with an average activity of ~0.8 mmol/g of alumina. After filtration and column chromatography, the slightly yellow crystalline enone **7** was isolated in 90% yield (Scheme 16). The oxidation was verified from the molecular ion in the mass spectrum of **7** as well as a carbonyl IR stretching frequency of 1693 cm^{-1} and ^{13}C NMR resonance at δ_C = 210.5 ppm. Melting point and spectroscopic data were also in agreement with the literature.[24] In enone **7**, the conjugative electronic displacement in the α,β-unsaturated carbonyl substructure affects the resonances of olefinic protons H-4 and H-5. The effect is stronger on H-5 than on H-4 due to orbital overlap and H-5 (*dd*, δ_H = 7.36 ppm) is shifted further downfield than H-4 (*dd*, δ_H = 5.77 ppm).

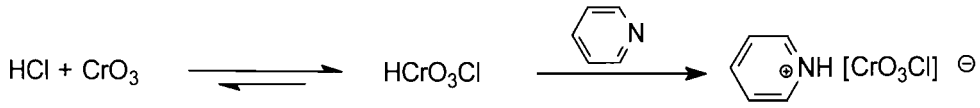


47 **48** (70%) **49** (90%) **7** (90%)

Scheme 16: a) $Mn(OAc)_3$, $KMnO_4$, KBr (cat.), AcOH, Ac_2O, 70^{0}C, 1 h; b) K_2CO_3, MeOH, room temp, 20 h; c) PCC/Alumina, hexane, room temp.

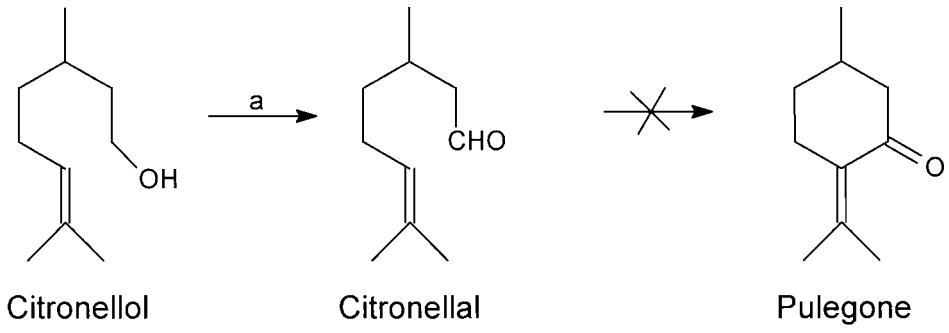
In the oxidation of alcohols to carbonyl compounds, many reagents containing chromium (IV) ion have been studied. However, a large number of them cannot be conveniently used for the oxidation of complex or highly sensitive substances.[29,30] For example, Collin's reagent (chromium trioxide/pyridine) is unstable, hygroscopic and is used in large excess. In addition, it has poor selectivity in the oxidation of primary alcohols to aldehydes.[29] Pyridinium chlorochromate (PCC), the reactivity of which has been studied by Corey and co-workers, on the other hand is a mild and versatile oxidant.[29] Addition of

chromium trioxide to hydrochloric acid (6N) furnishes unstable chlorochromic acid. Subsequent addition of pyridine gives non-hygroscopic pyridinium chlorochromate (PCC) as a yellow orange solid (Scheme 17).[29]



Scheme 17:

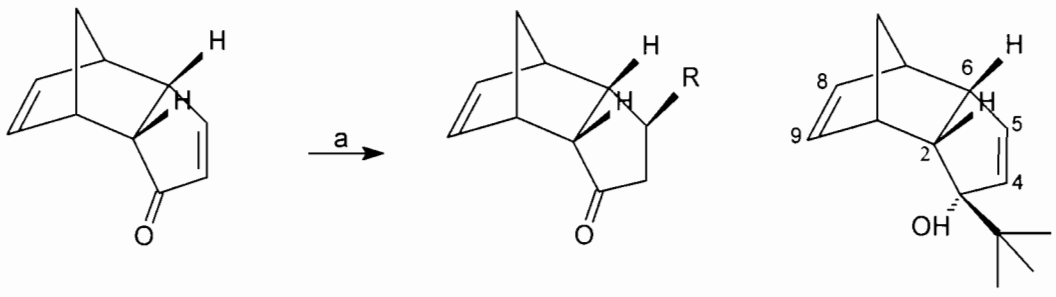
Cheng and co-workers reported pyridinium chlorochromate (PCC) adsorbed on alumina as a suitable reagent for the oxidation of alcohols to aldehydes and ketones. The reagent is prepared by adding alumina to pyridinium chlorochromate solution and removing the solvent under reduced pressure. The yellow-orange solid is kept at room temperature and stored in the dark.[30] The adsorbed reagent provides a reaction environment capable of enhancing the reactivity of numerous alcohols and has the added advantage of insolubility in the reaction media and ease of reaction work-up which is reduced to mere filtration. The slightly acidic character of pyridinium chlorochromate (PCC) requires buffering the reaction mixture with powdered sodium acetate to avoid oxidation of citronellol to pulegone. By comparision citronellol is directly oxidized to citronellal with pyridinium chlorochromate adsorbed on alumina without oxidizing to pulegone (Scheme 18).[29,30]



Scheme 18: a) PCC/Alumina

2.2. 1,4-addition of organocuprates:

With an efficient synthesis of **7** in hand, we turned our attention to examining the conjugate-addition reactions of organocuprate reagents (R_2CuM and RM/Cu^+, (M = Li or MgX) with **7**. These reagents are highly reactive and were expected to stereospecifically transfer ligands exclusively at the β-position of enone **7** to give *exo*-5-substituted tricyclodecenones (Scheme 19).[32,33] With Grignard reagents, copper works by transmetallating the reagent to give a soft organocopper reagent RCuMgX which undergoes conjugate addition to **7**.[32] The conjugate addition of five organometallic reagents to **7** was then explored under standard experimental conditions and the results are summarised in Scheme 19.



7 **50-54** **55**

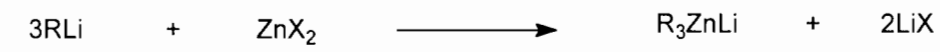
Scheme 19: a) $R_2CuLi/RCuMgBr$, Et_2O, -78^{0}C / room temp (R=Ph), 1-2 h, **50** (R=Bu^n, 92%), **51** (R=Ph, 95%), **52** (R=Me, 90%), **53** (R=Et, 80%), **54** (R=Bu^t, 42%)

In all cases, except with Bu^t_2CuLi which also gave a 1,2-addition product, the expected 1,4-addition products were obtained in excellent yield. This was confirmed from the ^{13}C NMR spectra of **50**, **51**, **52**, **53** and **54** which showed diagnostic carbonyl peaks at δ_C = ~ 220 ppm. The reaction with Bu^t_2CuLi not only gave the 1,4-addition product **54** in 42% yield, but the 1,2-addition alcohol **55** was also isolated in 15% yield. At room temperature, the reaction of Bu^t_2CuLi with **7** resulted in an increase in the yield of **55** and complicated the separation of **54** and **55** by chromatography. The structure of **55** was confirmed by noting the signals at δ_H = 6.17, 5.83, 5.56, and 5.50 ppm which

correspond to the four olefinic protons (Scheme 19). In addition, a broad singlet peak at δ_H = 1.27 ppm for the hydroxyl proton and the absence of a carbonyl peak in the ^{13}C NMR supported the formation of **55**.

Zwanenburg[33] *et al.* reported that Bu^s_2CuLi failed to yield a reasonable amount of the desired product on 1,4-additions to **7** at temperatures - 78^{0}C to 0^{0}C. They reasoned thermal instability of the reagent for this outcome. The above reason in addition to the steric hindrance exerted by the bulky Bu^t group could be contributing factors for the poor performance of Bu^t_2CuLi on conjugate addition to enone **7**. In a separate experiment, the reaction of 1.2 equivalents of B^tuLi with **7** at -78^{0}C in ether gave **55** in 55% yield.

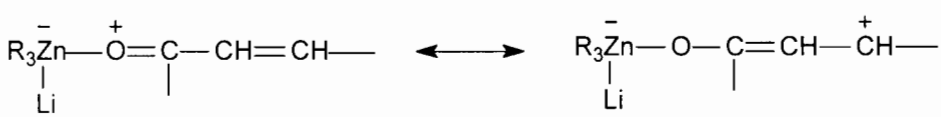
An alternative procedure reported by Isobe and co-workers[35] makes use of THF or ether solutions of lithium trialkylzinc reagents (R_2ZnLi). These reagents are prepared by stirring a suspension of $ZnCl_2$ (in TMEDA) or a solution of $ZnCl_2$-diethyl ether complex with a three-fold molar amount of the appropriate organolithium reagent at 0^{0}C for 15 min (Scheme 20).



Scheme 20:

Using the chemistry in Scheme 20, triorganozincate B^tu_3ZnLi was prepared from a saturated THF solution of $ZnCl_2$ and *t*-BuLi in a 1:3 mole ratio and stirred with **7** for 1 h at -70^{0}C. After work-up and column chromatography, the desired 1,4-addition product **54** was isolated as the sole product in 54% yield and the starting material recovered in 15%.

Regarding the mechanism of this reaction, it has been speculated that the primary interaction of the carbonyl group with Zn results in formation of a complex (Scheme 21) in which the **R** group obtains additional anionic activation to undergo transfer to the sterically accessible β-carbon.[35]



Scheme 21:

Interestingly, while addition of Ph_2CuLi at room temperature gave **51** in >90% yield, conducting the reaction at -78^{0}C gave **51** in 65% yield in addition to unidentified products. It has been proposed that the initial step in the reaction of organocuprates with enones involves a single electron transfer from the organocopper (I) species to the enone. This results in the formation of an enone radical anion and a cationic organocuprate radical $[R_4Cu_2Li_2]^{+\cdot}$. For R=Me and Bu^n, the cationic radical is unstable and product formation is kinetically controlled whereas for R=Ph, the cationic radical is longer living and product formation is thermodynamically controlled.[33] Conducting the experiment for R=Ph in the time frame described in Scheme 19 hence resulted in a slower rate of anionic radical interception and low yield for **51**.

In all 1,4-addition products **50**, **51**, **52**, **53** and **54**, a two-bond geminal coupling constant of ^2J = 18.35 - 20.10 Hz was observed between the H-4$_{endo}$ and H-4$_{exo}$ methylene protons. This type of coupling only appears when the two protons attached to the same carbon are diastereotopic and magnetically non-equivalent.[31] A second two-bond coupling with a much smaller coupling constant (in the range of J = 6.77 - 8.44 Hz) was observed between protons H-10$_a$ and H-10$_b$. With regard to H-4$_{exo}$, the assignment is deduced from its long-range four bond ***W*** coupling with proton H-2. The ***W*** geometry is the most effective arrangement for a four-bond orbital overlap,[31] and consistently gave rise to a coupling constant in the range of 1.70 -1.83 Hz (Figure 8).

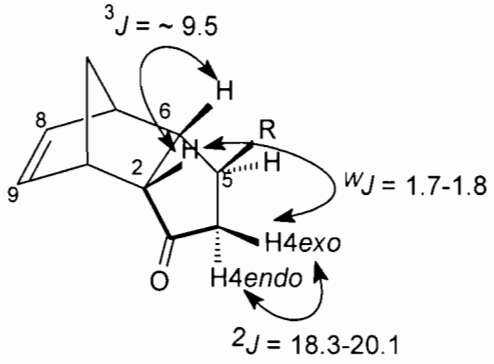


Fig. 8

Another interesting observation with the 1,4-addition products was the signal for H-5 of **51**. The H-5 signal resonated at δ_H = 1.64 -1.89 ppm for **50**, **52, 53**

and **54**. In **51**, the signal for H-5 was shifted downfield to δ_H = 2.92 ppm. The aromatic ring electrons create an induced magnetic field that opposes the applied field at the centre of the ring, but reinforce it outside the ring.[31] The effect is to deshield the hydrogens attached to the aryl carbons, which generally come in to resonance δ_H = 1.50 - 2.00 ppm downfield from olefinic signals. The close proximity of proton H-5 in **51** to the induced field is thus the cause for the downfield shift observed for H-5.

The factors affecting the stereochemistry of organocuprate additions to polycyclic enones are not completely understood.[33] Approach of the reagent is in general perpendicular to the plane of the enone and is sensitive to steric as well as stereoelectronic factors. The *exo*-1,4-addition of organocuprates to tricyclodecadienone **7** shown in Scheme 19 is mainly subject to the three dimensional structure of **7**. Because of the shielding of the concave face by the norbornene C_8-C_9 ethylene-bridge, attack of the reagent at this side of the molecule is severely restricted. Addition preferably occur at the sterically less-hindered convex face leading to 5-*exo*-substituted tricyclodecadienones.[33] Spectroscopic data also supported these structural assignments.

The interaction between nucleophiles and electrophiles is governed by two related interactions: electrostatic attraction between positive and negative charges and orbital overlap between the HOMO of the nucleophile and the LUMO of the electrophile. Nucleophiles containing small, electronegative atoms (such as O or Cl) tend to react under predominantly electrostatic control. On the other hand, nucleophiles containing larger atoms (including the sulfur of thiols, but also P, I, and Se) are predominantly subject to control by orbital overlap. The terms hard and soft are coined to describe these two types of reagents. Hard nucleophiles have higher charge density, while soft nucleophiles are either uncharged or have larger atoms with higher energy, more diffuse orbitals. Electrophiles too are classified as hard or soft. The small and charged H^+ for example, is classified as a hard electrophile while Br_2 is a soft electrophile; its orbitals are diffuse and it is uncharged. The carbon atom of a carbonyl group is also a hard electrophile because it carries a partial positive charge. In general, hard nucleophiles prefer to react with hard electrophiles, and soft nucleophiles with soft electrophiles.[69] In α,β -

unsaturated carbonyl compounds, conjugation leads to stabilizing interaction and modified reactivity and the π-bonds no longer react as independent functional groups but as a single, conjugated system. Delocalisation of the π-electrons over the four atoms in the conjugated system polarises the structure making the C=C bond electrophilic.[34] As shown in Figure 9, the true structure lies in between the two extremes. There are two electrophilic sites, one of which is hard and the other soft. The carbonyl group has a high partial charge on the carbonyl carbon and will tend to react with hard nucleophiles, such as organolithium and grignard reagents to give allylic alcohols in a 1,2-addition. Conversely, the β carbon of α,β-unsaturated carbonyl system does not have a high partial positive charge but is the site of the largest coefficient in the LUMO. This makes the β-carbon a soft electrophile and likely to react well with soft nucleophiles such as organocopper reagents in a 1,4-addition manner.

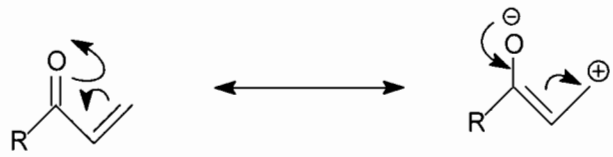


Fig. 9

A detailed orbital interaction diagram of methoxide nucleophile and acrolein enone is given in Figure 10 as an example.[69] Oxygen distorts the orbitals in the π-system of acrolein. In the LUMO, the largest coefficient is on the β-carbon of the α,β-unsaturated system (shown with an asterisk) and is the site of nucleophilic attack. The second largest coefficient is on the C=O carbon atom and it is not surprising that some nucleophiles attack here as well depending on the conditions of the reaction. Thus the actual bond-forming step must involve movement of electrons from the HOMO of the nucleophile to the LUMO of the unsaturated carbonyl compound.[69]

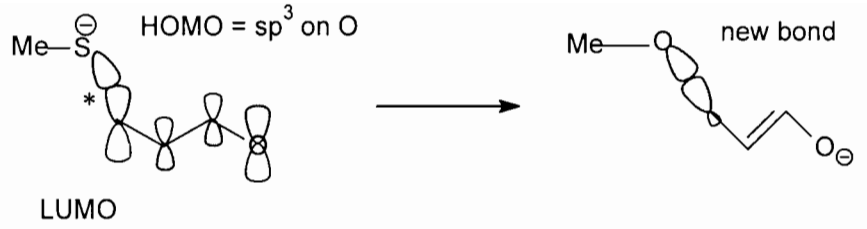
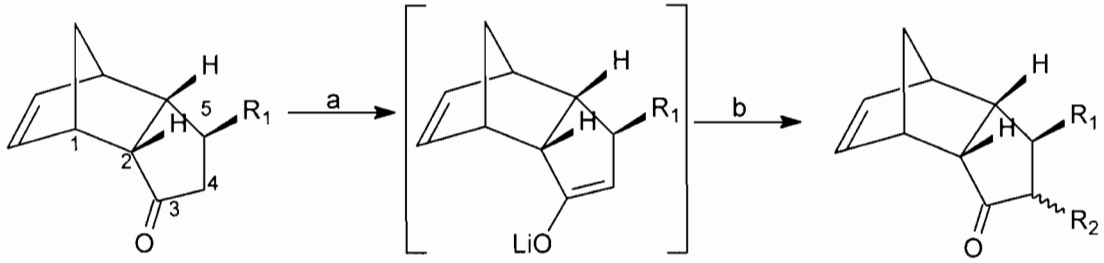


Fig. 10

2.3. Selective α-alkylation of *exo*-5-substituted tricyclodecenones with alkyl halides

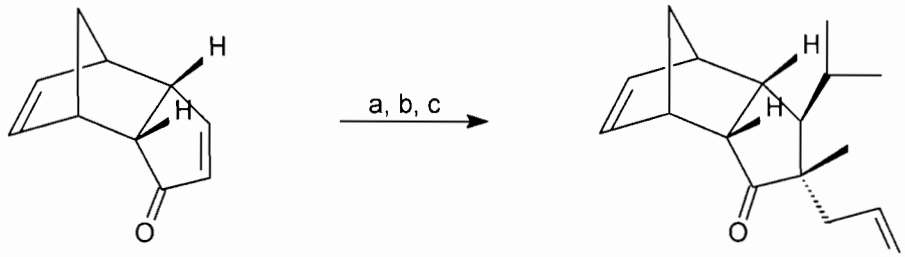
Having established efficient routes to *exo*-5-substituted tricyclodecenones (Scheme 19), attention was focused on elaborating these products for α-substitution at C-4 of the cyclopentanone moiety to give derivatives of type **56** (Scheme 22). A useful method for accomplishing this objective is the reaction of an alkylating agent with a particular structural isomer of an enolate anion.[44] The problem which limits the use of non-symmetrical α,α'-enolisable ketones such as **50** is the regioselective formation of their corresponding enolates.[47] One method of forming such enolates is to deprotonate a carbonyl compound with a base under kinetic or thermodynamic condition. Kinetic enolates are generated under non-equilibrating conditions by slow addition of a ketone to an excess of base at low temperature and usually the less hindered proton is abstracted. In making the kinetic lithium enolates, lithium diisopropylamide (LDA) generally gives the best selectivity.[44,45,46] On the basis of steric factors and choice of base (LDA), **50** was expected to undergo alkylation at the less hindered C-4-position under kinetic deprotonation conditions (Scheme 22).



50 (R_1 = Bu^n) **56** (R_1 = Bu^n, R_2 = Et)

Scheme 22: a) LDA, THF, -78^{0}C, 30 min. b) ethyl bromide, -78^{0}C – room temp

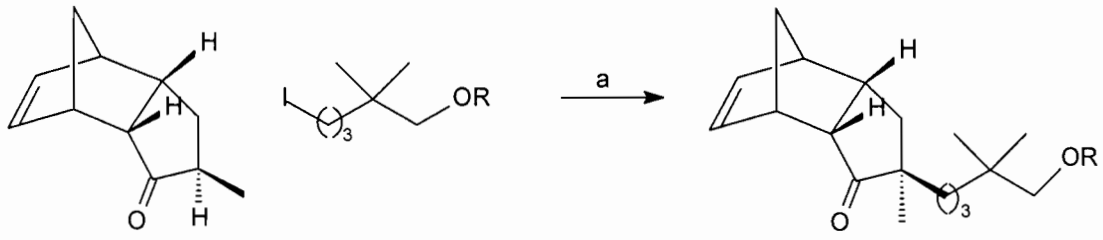
Thus, ketone **50** (R = Bu^n) was added slowly to LDA in THF at -78^{0}C and stirred for 30 min before rapid addition of the ethyl bromide. The reaction mixture was usually warmed to room temperature and in some cases stirred for more than 48 h. Upon work-up of these reactions, only the starting material **50** was isolated. There was no evidence of forming the C-4 substituted products. Even in the presence of a strong cation solvating agent hexamethylphosphoramide (HMPA) (30% co-solvent), the lithium enolate intermediate proved inert towards the alkyl halide. Further attempts were made to form the enolates at 0^{0}C but this also failed to give the desired product upon addition of the alkyl halide. These results contrast with those obtained by Goverdhan *et al.* on their stereoselective approach to the hydroazulenic core of the diterpene antibiotic guanacastepene A. They demonstrated successful α-alkylation (C-4) of the product of 1,4-addition isopropylmagnesium iodide to enone **7**. α-Alkylation with allyl bromide (LDA base) furnished a mixture (~60:40) of *endo*- and *exo*-isomers, whereas the second α-alkylation with methyl iodide (NaH base) yielded only a single product with methyl alkylation occurring exclusively from the *exo*-face (Scheme 23).[50]



7 **57**

Scheme 23:a) ^{i}PrMg, CuI, Et_2O, 0^{0}C, 20 h, 90%, b) LDA, THF, HMPA, Allylbromide, 60%, c) NaH, THF, MeI, 82%.

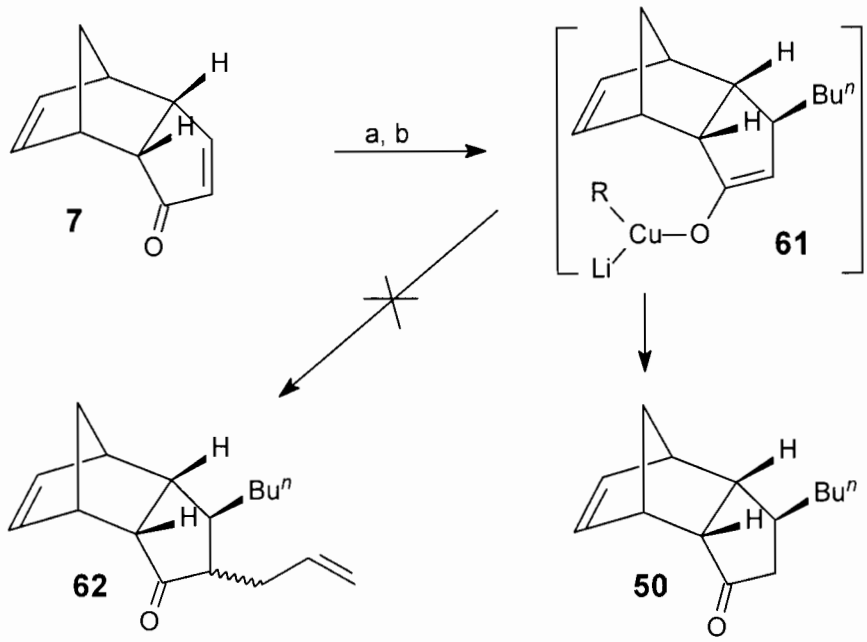
In one of their steps towards the total synthesis of the antifungal natural product Culmorin, Takasu and co-workers were able to α-alkylate **58** which only has a methyl substitution at C-4.[51] They used $NaCH_2S(O)CH_3$ as a base and iodide **59** as the electrophile to get **60** in 94% yield (Scheme 24).



58 **59** **60**

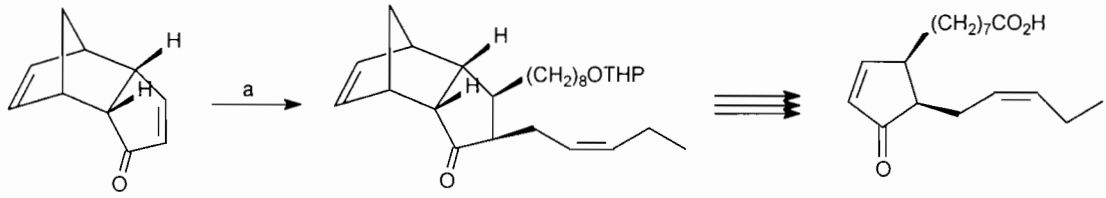
Scheme 24: a) $NaCH_2S(O)CH_3$, **59**, 94%

Given these precedents, attention was then turned to the utility of lithium organocuprate reagents in conjugate additions.[43] The intermediate formed prior to work up has anionic character as shown by isolation of various enol derivatives following treatment with appropriate electrophilic reagents.[52] This approach involves conjugate addition followed by *in situ* trapping of the derived enolate by an electrophile (Scheme 25). Enone **7** was stirred with $Bu^n{}_2CuLi$ for 2 h at room temperature and quenched with excess allyl chloride. After work-up and purification of the reaction mixture, only the 1,4-addition product **50** was isolated in 80% yield.



Scheme 25: a) $Bu^n{}_2CuLi$, Et_2O, room temp, 2 h b) Allyl chloride, room temp, 2 h.

Scheme 25 represents a three-component coupling process designed to generate a nucleophilic enolate for substitution with allyl chloride (at C-4 of **61**). Facile double-bond shift of copper/lithium enolates *via* intermolecular protonation/deprotonation equilibration in the presence of proton sources is thought as the reason for the failure to alkylate **61**. It was only with the aid of triphenyltin chloride transmetalation of enolates generated from organocuprate conjugate additions to 4-oxygenated-2-cyclopentenones, that Noyori *et al.* were able to overcome enolate equilibrations resulting in efficient alkylation with alkyl halides.[54] In Scheme 26, the first step in the total synthesis of 12-oxophytodienic acid (12-oxoPDA) **64** was only successful when the enolate generated from the reaction of a mixed cyanocuprate reagent and **7** was transmetalated with Bu_3SnCl. The triorganotin halide reduced the basicity of intermediate enolate to effect substitution with pentenyl iodide. In spite of the steric hindrance exerted by the *exo*-substituent at C-5, **63** was exclusively obtained as the *exo-cis*-disubstituted isomer.[53]



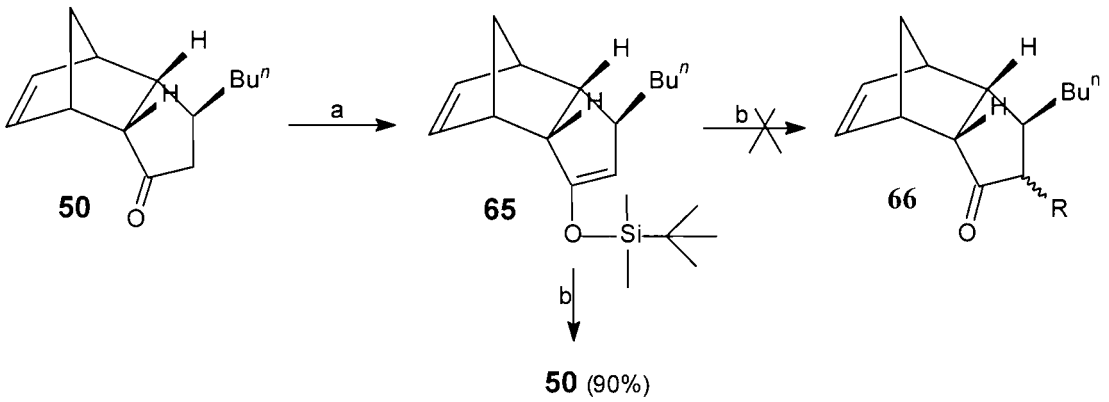
7 **63** **64**

Scheme 26: a) $Li_2[Cu(CH_2)_8]OTHP]CN$, (Z)-pent-2-enyl iodide, Bu_3SnCl, HMPA

In concert with other reports, Heng and Smith attempted to activate **61** (Scheme 25) by complexation with copper (I) ligands or by operating in a more "activating" solvent (dimethoxyethane, tetrahydrofuran). However their procedure resulted in unacceptable yields for the conjugate addition step.[52]

The third approach investigated in this dissertation was to generate the kinetic enolate from the reaction of **50** with lithium diisopropylamide (LDA) and trap the enolate with *t*-butylchlorodimethylsilane (TBDMSCl) to form silyl enol ether **65**. Nucleophilic cleavage of the Si-O bond in the presence of an alkyl halide was expected to yield alkylation of **65** at C-4 (Scheme 27). Though the enolate-trapping reactions of TBDMSCl closely parallels those of

chlorotrimethylsilane (TMSCl), TBDMSCl was used in this reaction (Scheme 27) since TBDMS ethers are more stable than TMS ethers.[57] Ketone **50** was added slowly to a THF solution of LDA (2 equiv.) at -78 ^{0}C and stirred for 30 min before the rapid addition of TBDMSCl. The reaction was brought to room temperature and the colourless, non-polar (TLC) silyl enol ether **65** was isolated in 50% yield after column chromatography. A complex mixture of polar materials was also recovered in considerable amount. In the down-field region of the ^{1}H NMR spectrum of **65**, a two-proton *m* for H-8 and H-9 (δ = 6.03-5.99 ppm) and a one-proton *m* for H-4 (δ = 4.34 ppm) were observed for these olefinic protons. In the highfield region, a 9 H, and a pair of 6 H *s* peaks at δ = 0.93 ppm and (δ = 0.14 and 0.13 ppm) respectively were also in agreement with the presence of the silyl enol ether group. The appropriate position and number of ^{13}C peaks in addition to mass and IR (1013 cm^{-1} (O-Si)) spectra further supported the structure of **65**.



Scheme 27: a) LDA, TBDMSCl, THF, - 78^{0}C - room temp, 50% b) TBAF, benzyl bromide, MS (4 Å), THF, - 78^{0}C - room temp, 5 h.

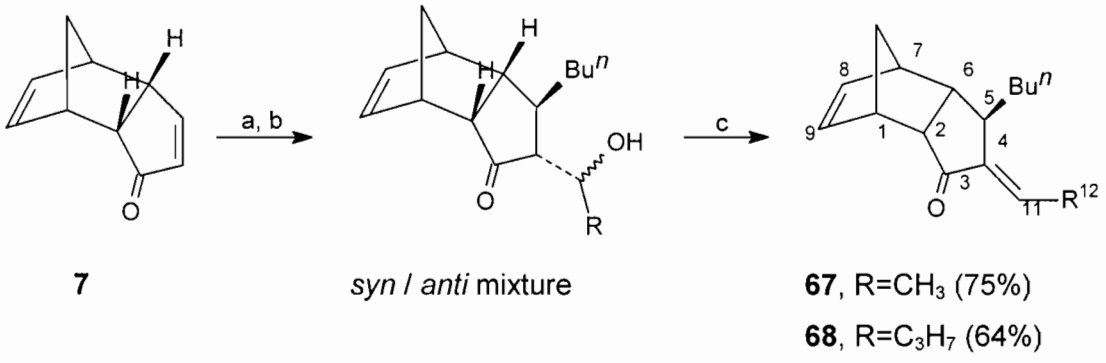
Schemes 22 and 25 showed the inertness of the lithium enolates generated from the reaction of **50** with LDA and the Gilman reagent (Bu^n_2CuLi) towards alkyl halides. Substitution of the counter cation to quaternary ammonium is known to activate the enolate anion and make alkylation more feasible.[55] Among quaternary ammonium fluoride salts, tetra-*n*-butylammonium fluoride (TBAF) has found widespread use as a reagent to promote desilylation reactions under anhydrous conditions.[56] Thus the fluoride ion-induced

reaction of silyl enol ether **65** with tetra-*n*-butylammonium fluoride (TBAF) in the presence of an alkyl halide was investigated in order to avoid undesirable proton transfer. The expectation was that TBAF would cleave the silicon–oxygen bond of silyl enol ether **65** to give a quaternary ammonium enolate for α-alkylation with benzyl bromide (Scheme 27).[59]

TBAF (1.5 equiv.) was stirred overnight with molecular sieves, and the reaction performed by addition of a THF solution of silyl enol ether **65** and benzyl bromide to the TBAF-4Å molecular sieves suspension in THF. Unfortunately, the fluoride anion didn't effect the desired reaction between **65** and the alkyl halide. The parent ketone **50** was the only product isolated from this reaction mixture. This was presumably due to the extremely hygroscopic nature of tetra-*n*-butylammonium fluoride (TBAF). A complete removal of water from the fluoride ion is critical to the success of this kind of transformation. In connection with this, it is worth mentioning the work by Fry *et al.* on the instability of anhydrous tetra-*n*-alkylammonium fluorides. They concluded that it is very unlikely that pure, anhydrous tetraalkylammonium fluoride salts have ever, in fact, been produced in the case of ammonium ions that are susceptible to E2 elimination.[56] In another attempt using Lewis acid mediated alkylation, a mixture of silyl enol ether **65** and benzyl bromide in dichloromethane (DCM) was treated with titanium tetrachloride at -78^{0}C. After 30 min stirring, the reaction mixture was quenched and the parent ketone **50** again isolated as the only product. This affirms the idea that primary alkyl halides do not easily form cations when treated with Lewis acids ($TiCl_4$ in this case). In fact, direct alkylation of silyl enol ethers is mainly restricted to tertiary and allylic halides and acetates.[60] The difficulty of trapping enolate intermediates by alkyl halides have been recognized by many research groups.[54] Hence, more powerful α-side-chain electrophiles were explored and among these electrophiles, the use of aldehydes in the aldol condensation of magnesium enolate intermediates is described in the next scheme.

2.4. Aldol Condensation

Grignard reagents on conjugate addition to α,β-unsaturated carbonyl compounds produce magnesium enolates that are valuable intermediates for further transformation. The classical aldol condensation, which usually leads to a mixture, has been improved by condensing a preformed magnesium enolate with an aldehyde. Using this method, only the desired aldol is formed, even if it is the thermodynamically less stable isomer.[48] We intended to carry out the aldol condensation by making use of the magnesium enolate from the Cu (I)-catalysed conjugate addition of *n*-butylmagnesium bromide (Bu^nMgBr/CuI) to enone **7** (Scheme 28). To this end, enone **7** was stirred with Bu^nMgBr/CuI for 2 h at 0^0C, followed by a gradual addition of acetaldehyde at -15^0C. The reaction mixture was stirred at -15^0C and 0^0C for 1 h and 30 min respectively to give a mixture of two products as evidenced by TLC.



7 *syn* / *anti* mixture **67**, R=CH_3 (75%)
68, R=C_3H_7 (64%)

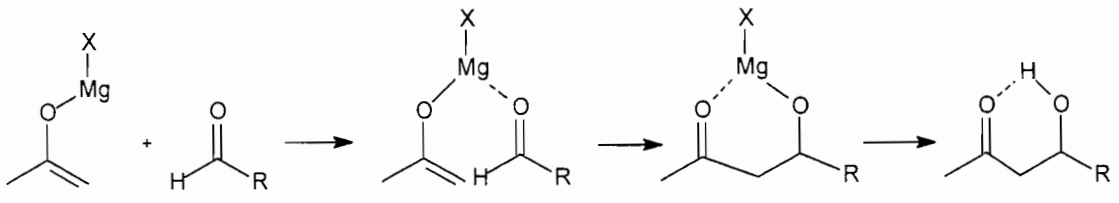
Scheme 28: a) Bu^nMgBr/CuI, Et_2O, 0^0C, 2 h b) RCHO, -15 - 0^0C, 1.5 h c) TsOH, toluene, reflux, 1 h.

Aldol condensations of systems like **7** with aldehydes produce two new β-ketols with adjacent chiral centres and thus the possibility of diastereoisomer formation which can have either the *syn* or *anti*-relative configuration (Scheme 28).[58] Owing to the labile nature of the β-ketols on column chromatography, they were dehydrated to the stable enone before purification was attempted. This was achieved by refluxing the mixture in toluene in a Dean-Stark apparatus in the presence of a catalytic amount of *p*-toluenesulphonic acid[61] for 1 h to give the corresponding enone **67** in 75% overall yield. A second

experiment using *n*-butyraldehyde as the electrophile gave enone **68** in 64% overall yield. When the reaction was performed with acetaldehyde, an excess (10 equiv.) of the aldehyde was generally used. For the less volatile *n*-butyraldehyde, two equivalents of the reagent were used.

The structures of enones **67** and **68** were ascertained from their NMR (^{1}H and ^{13}C), IR and mass spectra. The *exo*-stereochemistry for the butyl group at C-5 was assigned from the structure of **7** as previously stated. The shielding effect exerted by the C_8-C_9 ethylene-bridge severely hinders attack at the concave face and addition of Bu^{n}MgBr/CuI thus occurs at the sterically less hindered convex face leading to 5-*exo*-substituted **67** and **68**. Compared to proton H-5 of **50**, the signals from protons H-5 of **67** and **68** were shifted downfield by δ_H ~ 1.50 ppm as a result of the anisotropic deshielding (allylic) effect exerted by the high electron-density double bond.[31] Further downfield, a one proton *qd* (δ_H = 6.36 ppm, *J* = 7.3, 2.2 Hz) for H-11 of **67** and a *td* (δ_H = 6.27 ppm, *J* = 7.6, 2.3 Hz) for H-11 of **68** is appropriate for a β-olefinic proton of an α,β-unsaturated carbonyl system. In the upfield region, a 3-proton *dt* (δ_H = 1.72 ppm, *J* = 7.3, 1.1 Hz) signal with a major coupling to H-11 was observed for the allylic H-12 protons of **67.** A two-proton distorted AB multiplet resonance for the allylic H-12 protons of **68** was also observed in the range of δ_H = 2.11-1.92 ppm. The stereochemistry of the exocyclic-enone in **67** and **68** was assigned as the *E*-stereoisomer following similar work by Iqbal and Evans and no further work was done with the assignments.[49] Chemical shifts of δ_C = ~ 209, ~ 145, ~ 133-136, ~ 131-133 ppm for carbons: C3 (carbonyl), C11, C8 / C9 and C4 respectively were in agreement with the structures of **67** and **68**.

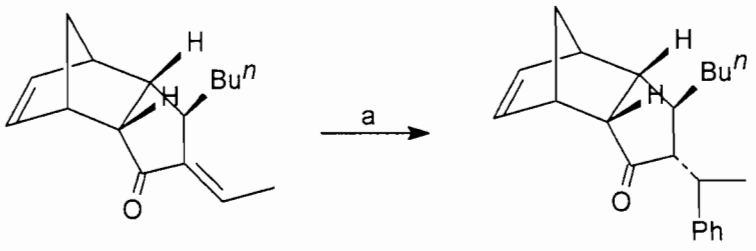
The mechanism of the condensation reaction is best interpreted following *House et al.* (Scheme 29).



Scheme 29:

Interaction of the acidic magnesium enolate with the basic aldehyde oxygen forms a loose complex, which reacts in a 6-membered transition state to give a keto-alkoxide as a stable magnesium chelate. The stability of magnesium chelates in non-polar solvents is high enough to prevent further, undesired transformations. Quenching the reaction with aq. NH_4Cl readily decomposes the magnesium enolate to give the free aldol.[48]

Previously, enone **7** was reacted with organocuprates $R_2CuLi/RCuMgBr$ (R= Bu^n, Ph, Me, Et and Bu^t) to give 1,4-addition products **50**, **52**, **53** and **54**. Since **67** is also an enone (exocyclic), the conjugate addition of Gilman reagent Ph_2CuLi to **67** in ether was also attempted by stirring the enone with 1.5 equiv. of the reagent at 0 ^0C for 2 h (Scheme 30). Despite the formation of two new chiral centers that could lead to four possible diastereomeric products, **69** was the only colourless crystalline solid product isolated (70%) after work-up and column chromatography.



67 **69**

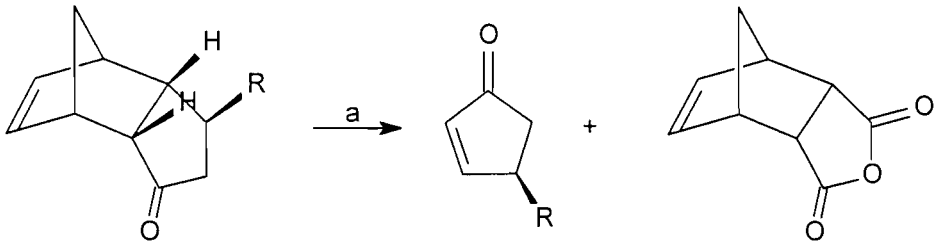
Scheme 30: a) Ph_2CuLi, Et_2O, 2 h, room temp, 70%.

The presence of a five-proton aromatic multiplet (δ_H = 7.27-7.11-ppm) and the disappearance of the *qd* (δ_H = 6.36 ppm) olefinic β-proton (H-11) signal of **67** confirmed the successful delivery of the phenyl group at the β-position. Two more observations about the proton spectrum of **69** are worth mentioning. The olefinic signals for H-8 and H-9 of **69** were well-resolved compared to H-8 and H-9 of **67**, which appeared as two overlapping *dd* peaks. The signal resolution of H-8 and H-9 is assumed to be a result of the influence exerted by the aromatic ring of the phenyl group. This effect can only be significant if the

phenyl group is at the *endo*-face of the molecule and the *endo*-relative stereochemistry is thus proposed for **69** *via* *exo*-protonation of the intermediate of the enolate on work-up (*via* enol). In a similar case which can be related to the stereochemistry of **69** at C-4, **68** was submitted to 1,4-hydride reduction with $Li(OBu\text{-}t)_3AlH$ to give the reduction product with the Bu^n group having the *endo*-stereochemistry.[53] The cycloreversion of substrates such as **69** demonstrates the usefulness of this sequence in the syntheses of PGA type compounds.

2.5. Retro-Diels-Alder reactions

Using the procedure reported by Grieco,[42] 1,2-dichloroethane solutions of *exo*-substituted tricyclodecenones **50**, **51**, **52** and **53** were treated with 1.1 equiv. of ethylaluminum dichloride ($EtAlCl_2$) in the presence of maleic anhydride (MA) and stirred for 1.5 h at 55^0C (Scheme 31).



50-53 **70-73** **27**

Scheme 31: a) $EtAlCl_2$, maleic anhydride, 1,2-dichloroethane, 55^0C, 1.5 h, **70** ($R=Bu^n$, 80%), **71** (R=Ph, 81%), **72** (R=Me, 50%), **73** (R=Et, 60%).

After work-up of the reaction mixtures, 4-substituted-2-cyclopentenones **70** - **73** were isolated in good yields after column chromatography (Scheme 32). Maleic anhydride (MA) forms the Diels-Alder adduct **27** with the liberated cyclopentadiene and shifts the reaction equilibrium toward the formation of the 4-substituted cyclopentenones. An ambient temperature cycloreversion attempt on **50** using 1.1 equiv. of ethylaluminum dichloride ($EtAlCl_2$) was only complete after a prolonged reaction time. However Grieco has reported[42] a 1 h room temperature cycloreversion reaction of **50** using 1.1 equiv. of

methylaluminum dichloride ($MeAlCl_2$) in the presence of maleic anhydride. Table 1 summarises the ^1H NMR data for the cyclopentenones **70-73**

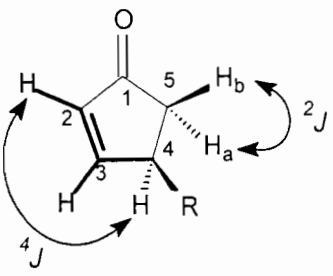


Fig. 11

Table 1; Chemical shifts (ppm) and coupling constants (Hz) for selected protons of **70-73**

	H-3, *dd*, ^3J, ^3J	H-2, *dd*, ^3J, ^4J	H-4, *dddd*, ^3J,^3J ^4J / *m*	H-5_a, *dd*, ^2J, ^3J	H-5_b, *dd*, ^2J, ^3J
70	7.64 (5.8, 2.5)	6.14 (5.8, 2.0)	2.94-2.83 (*m*)	2.53 (18.7, 6.4)	1.96 (18.7, 2.2)
71	7.71 (5.6, 2.5)	6.35 (5.6, 2.1)	4.18 (6.8, 2.4, 2.1)	2.90 (18.9, 6.8)	2.35 (18.9, 2.4)
72	7.53 (5.3, 2.5)	6.08 (5.3, 1.9)	3.17-2.77 (*m*)	2.59 (16.9, 6.5)	1.86 (16.9, 2.0)
73	7.65 (5.4, 2.5)	6.16 (5.4, 2.1)	2.93 (*m*)	2.53 (17.0, 6.7)	2.01 (17.0, 2.2)

The ^1H NMR data in Table 1 shows a pair of *dd* peaks for protons H-5_a and H-5_b with a large two-bond geminal (^2J) coupling constant. In the column for H-2, ^3J corresponds for coupling with H-3 while ^4J represents for a four-bond allylic-coupling with H-4 as shown in the cosy spectra of **71** (Figure 12). The ^3J for H-5_b is smaller in magnitude to ^3J for H-5_a because of its angular relation with H-4 (Table 1). Further downfield, coupling between olefinic protons H-2 and H-3 and a *m* peak for H-4 of **70**, **72** and **73** and a *dq* for **71** confirms the position of the double bond in the cyclopentenone ring as shown in Figure 11. It is also evident that the substantially deshielded H-3 signals resonate downfield to H-2 signals because of conjugation. The formation of the cyclopentenone ring in **70-73** was further confirmed from the correct number and position of ^{13}C NMR peaks, a carbonyl group IR absorption band (1750-1740 cm^{-1}) and mass spectra. No double bond rearrangement or decomposition associated with highly functionalised cyclopentenones[39] was observed with these compounds.

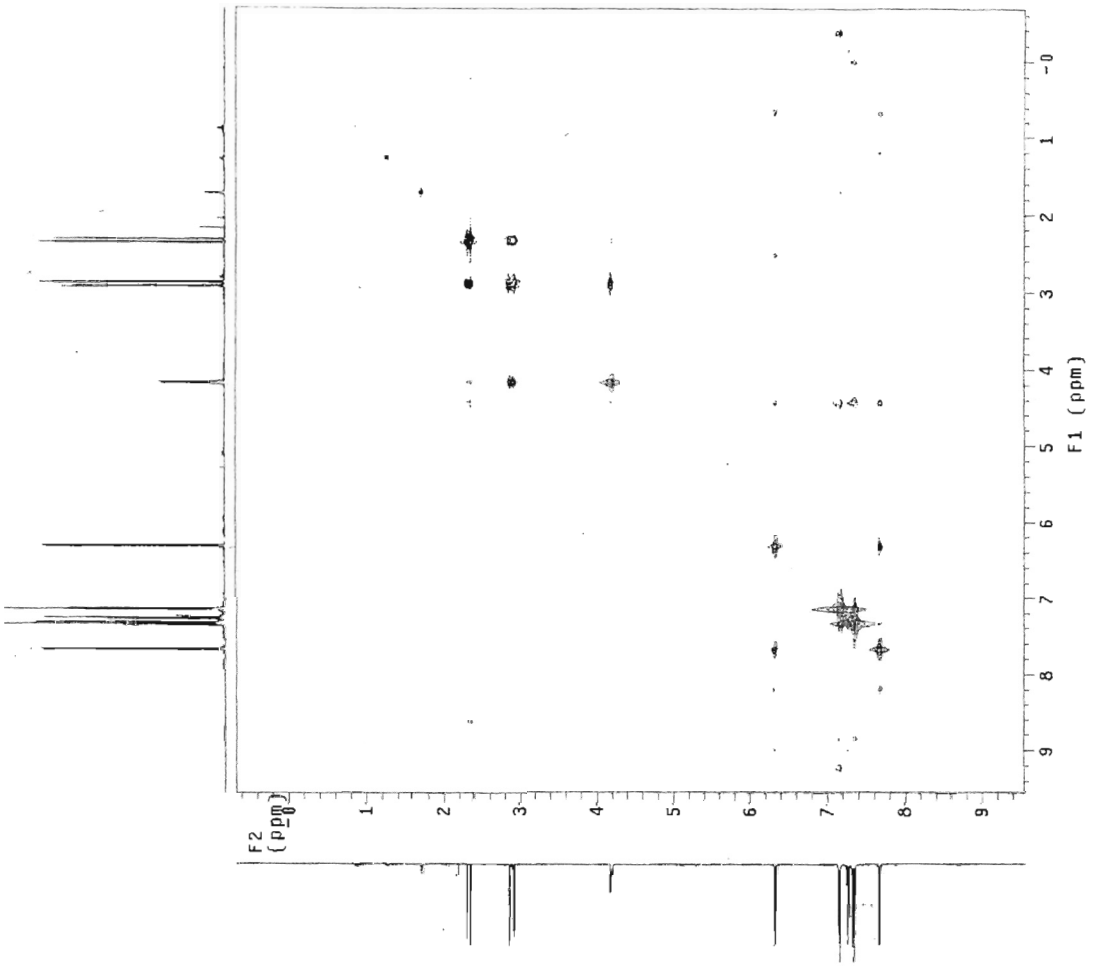


Figure 12: The cosy spectrum of **71**

To further explore the scope of this transformation with different Lewis-acids, *exo*-substituted tricyclodecenones **50** and **51** were submitted for cycloreversion at either room temperature or 55 ^{0}C (Table 2). These TLC-scale reactions were performed to determine the amount of catalyst and the reaction time with individual Lewis-acids. The reactions were run under nitrogen in 1,2-dichloroethane (DCE) and the progress followed by TLC.

Table 2 Reaction time and catalytic amount determination (TLC analysis)

#		L. acid (equiv.)	[a]ma, (equiv.)	T (^{0}C)	t (h)	[c]s.m
1	**51**	$EtAlCl_2$ (0.2)	2.0	55	2	trace
2	=	$EtAlCl_2$ (0.2)	4.0	55	15	=
3	=	$EtAlCl_2$ (0.5)	2.0	55	15	=
4	=	$EtAlCl_2$ (0.5)	2.0	rt	1.5	Majority
5	=	$EtAlCl_2$ (0.8)	4.0	55	1.5	trace
6	**50**	$EtAlCl_2$ (1.1)	1.5	rt	4	none
7	=	$EtAlCl_2$ (1.2)	1.5	55	1.5	=
8	**51**	$EtAlCl_2$ (1.2)	5.0	55	1.5	=
9	**50**	$TiCl_4$ (0.2)	0.2	55	16	considerable
10	=	$TiCl_4$ (1.3)	4.0	rt	3	trace
11	=	$BF_3.Et_2O$ (3.0)	5.0	55	1.5	none
12	=	$BF_3.Et_2O$ (3.0)	0.0	rt	6.0	considerable
13	=	$SnCl_4$ (0.2)	2.5	rt	1.5	majority
14	=	$SnCl_4$ (0.2)	3.0	rt	15	considerable
15	**50**	$Ti[OCH(CH_3)_2]_4$ (0.2)	3.0	rt-55	15	all
16	**51**	[b]$AlCl_3$ (0.2)	2.5	55	3	all

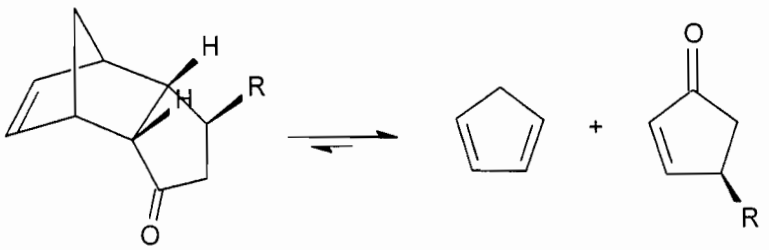
a) maleic anhydride was dried with P_2O_5 prior to use.

b) the activity of $AlCl_3$ as a catalyst depends on the purity and degree of hydration and hence was subjected to purification by sublimation prior to use.[43]

c) remaining starting material.

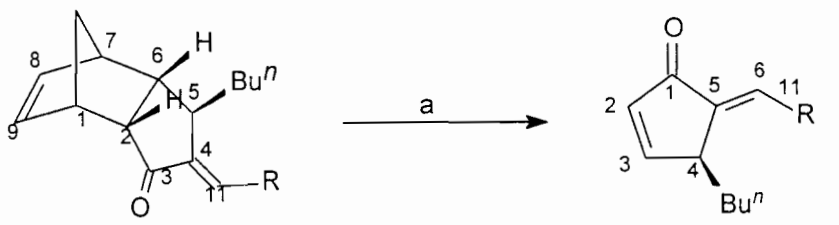
Table 2 shows the rate of cycloreversion of **50** and **51** to **70** and **71** respectively when several Lewis acids are utilized in excess and sub-stoichiometric amount relative to substrate. The highest rate of cycloreversion using sub-stoichiometric amount of the acid was observed when $EtAlCl_2$ was used as a catalyst. This is followed by $TiCl_4$ and $SnCl_4$. Using 1.1-1.2 equiv. of

$EtAlCl_2$, the reactions were complete in 1.5 h and 4 h at 55^0C and room temperatures respectively. With 0.2-0.8 equiv. of $EtAlCl_2$, a reasonable amount of the product was only obtained at high temperature and long reaction time. When $BF_3.Et_2O$ was used as the Lewis-acid, a large excess equiv. of the acid was generally needed to drive the reaction to completion. In a related work, Marchand *et al.*[40] reported the use of $BF_3.Et_2O$ in the absence of added dienophile. Treatment of **50** with 3 equiv. of $BF_3.Et_2O$ in the absence of maleic anhydride was only 50% complete after a 6 h room temperature stirring. $AlCl_3$ was first subjected to purification by sublimation (x 2) prior to use. In spite of repeated attempts, no cycloreversion results were obtained when $AlCl_3$ was used as the catalyst. We assume the extremely hygroscopic nature of $AlCl_3$ to be responsible for failing to effect the desired cycloreversion. The same result was also obtained when $Ti[OCH(CH_3)_2]_4$ was used. When the sub-stoichiometric $EtAlCl_2$-catalysed reactions were monitored (TLC) in 20 min intervals, an interesting phenomenon regarding the consumption of the starting material was observed. During the course of the first intervals of reaction, the starting material was completely consumed in one interval and partially regenerated in the next interval. This shows the cycloaddition of the cyclopentenone with liberated cyclopentadiene to regenerate the starting material and indicates the presence of a dynamic equilibrium between the retro-Diels-Alder and Diels-Alder reactions depicted in Scheme 32.



Scheme 32:

In a separate experiment, enones **67** and **68** were also treated with ethyl aluminium dichloride ($EtAlCl_2$) in the presence of maleic anhydride and stirred at 50^0C. After 1.5 h stirring, the corresponding $\alpha\alpha'$,$\beta\beta'$-unsaturated dienones **74** and **75** were isolated in 75 and 65% yield respectively (Scheme 33).



67, R=CH_3 **74**, R=CH_3 (65%)

68, R=C_3H_7 **75**, R=C_3H_7(75%)

Scheme 33: a) $EtAlCl_2$, Maleic anhydride, 1, 2-dichloroethane, 50^{0}C, 1.5 h

The structures of **74** and **75** were confirmed from NMR (^{1}H and ^{13}C), IR and mass spectra. A signal for H-3 (δ_H = ~ 7.53 ppm) with a *ddd* multiplicity for both **74** and **75** was assigned to the β-proton of the endocyclic α,β-conjugated carbonyl functionality. Besides the vicinal coupling of H-3 to H-2 (J = ~ 6.0 Hz) and H-4 (~ J = 2.7 Hz), a long range coupling of J = ~ 1.0 Hz with the first methylene protons of the Bu^n group was established from the cosy spectra of **74** and **75** (Figure 13). Further upfield, a *qt* (δ_H = 6.61 ppm) for the β'-proton (H-6) of **74** and a *t* (δ_H = 6.53 ppm) for the β'-proton (H-6) of **75** was in agreement with the proposed structures. This was further confirmed from a three-proton *d* signal for H-11 of **74** and a two-proton highly distorted double multiplet AB system for H-11 of **75**. The additional coupling (J = ~ 2.0 Hz) observed for the α-proton (H-2) for **74** and **75** is due to the allylic coupling to H-4. The proton resonance of H-4 falls within the range δ_H = ~ 3.52-3.41 ppm for both **74** and **75**. The presence of H-4 also revealed that isomerization of the exocyclic double bond in to the ring had not taken place. The ^{13}C NMR signals at δ_C 196.7 (CO), 161.8 (C3), 139.2 (C6), 134.7 (C2), and 130.2 (C5) of **74** were in agreement with its structure. All the ^{13}C NMR peaks for **75** were also in agreement with its structure.

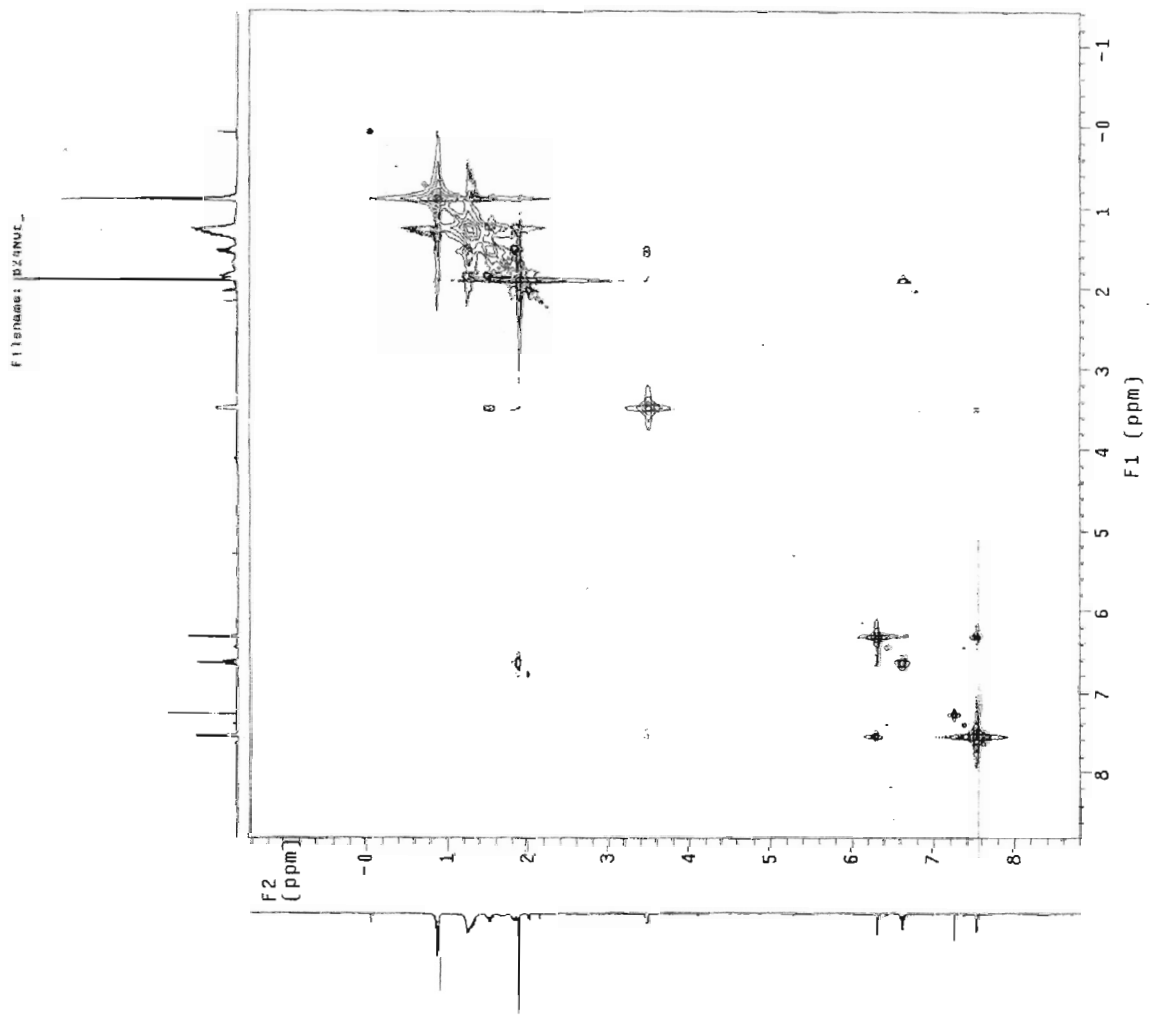


Figure 13: The cosy spectrum of **74**

2.5.1. Asymmetric chiral Lewis-acid catalysed retro Diels-Alder reactions

Several efforts on the development of asymmetric Diels-Alder reactions have focused the use of chiral Lewis-acids in the synthesis of optically pure five membered rings.[65,67] The enantioselective synthesis of substituted cyclopentenones still relies on enzymatic kinetic resolutions[36,37] or involves the use of chiral starting materials.[38] In view of this and the ongoing development in asymmetric catalysis, we intended to make use of *in situ*-prepared chiral Lewis-acids in the asymmetric synthesis of cyclopentenones *via* the retro-Diels-Alder reaction. In this regard, the necessity to determine the enantiomeric composition (*ee*) on relatively small samples required a reliable method.

The determination of enantiomeric purity using NMR requires the use of a chiral auxiliary that converts a mixture of enantiomers into a diastereoisomeric mixture. Providing there is a large enough chemical shift non-equivalence to give-base line resolution, integration gives a direct measure of diastereoisomeric composition which can be related directly to the enantiomeric composition of the original mixture.[70] Three types of chiral auxiliaries are commonly used. Chiral lanthanide-shift reagents (CLSR) and chiral solvating agents (CSA) form diastereoisomeric complexes *in situ* with substrate enantiomers and may be used directly. Chiral derivatizing agents (CDAs) on the other hand require the separate formation of discrete diastereoisomers and remain the most widely used NMR technique for enantiomeric purity assay.[70]

Chiral Lanthanide-shift reagents promote, in addition to the usual lanthanide-induced shift (LIS), $\Delta\delta$ 'enantiomeric shift differences', $\Delta\Delta\delta$ values. These values are determined experimentally by successively adding small quantities of the shift reagents and examining the spectrum of the solution after each addition. Magnitudes of $\Delta\delta$ and $\Delta\Delta\delta$ depend on the ratio of the shift-reagent to substrate. The frequency separations between the signals define the enantiomeric-shift difference, $\Delta\Delta\delta$.[70,71,72] A central problem with this procedure could arise from broadening of signals, aggravating the exact determination of peak positions and chemical shifts.[71]

Among chiral derivatizing agents (CDAs), Mosher's acid (α-methoxy-α-(trifluoromethyl)phenylacetic acid, MTPA) continues to be a popular chiral derivatizing agent for the determination of enantiomeric purity of alcohols and amines (Figure 14).[72]

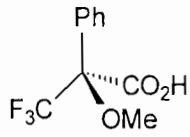
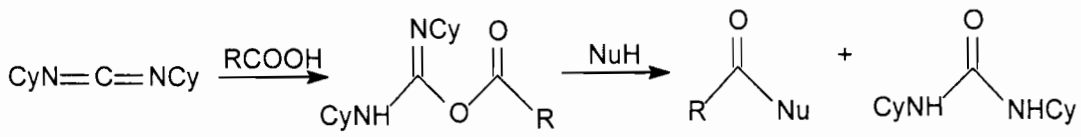


Fig. 14

The amide and ester derivatives formed may be analysed by chromatographic (HPLC, GC, TLC, etc.) or spectroscopic (^{1}H NMR, ^{19}F NMR, etc.) methods.[70] If the compound has a complex ^{1}H NMR spectrum, the presence of the trifluoromethyl group permits the use of uncongested fluorine NMR spectrum. MTPA is generally reliable and because there is no hydrogen α to the carboxyl group, racemization during derivatization is impossible.[70,74] MTPA reacts directly with amines and alcohols in the presence of condensing agents such as 1,3-dicyclohexylcabodiimide (Scheme 34).[74]



Scheme 34:

In an attempt to establish a reliable method, we first applied the chiral lanthanide-shift reagents [Eu(hfc)$_3$] and [Eu(tfc)$_3$] to ketones **50**, **51** and **71.** In all experiments, to a $CDCl_3$ solution of substrate was successively added small quantities of the shift-reagent and the spectra captured in a 200 ^{1}H MHz NMR after each addition. The results from [Eu(tfc)$_3$] and [Eu(hfc)$_3$] additions to ketones **50**, **51** and **71** showed no evidence of enantiomeric-shift differences, $\Delta\Delta\delta$ even after a 10% shift-reagent to substrate, mole-ratio addition. On further additions, the measurement of the lanthanide-induced

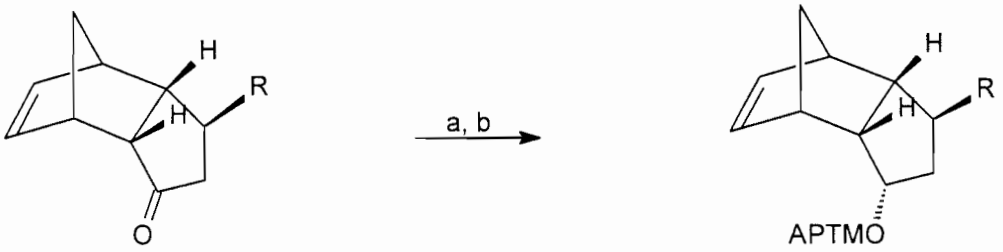
shift (LIS), $\Delta\delta$ was complicated due to signal broadening. The next substrate of choice was acetate **48**. The acetate methyl protons are close to the coordination site and a certain degree of enantiomeric-shift differences $\Delta\Delta\delta$ was expected for these protons. After successive additions of $[Eu(tfc)_3]$, the acetate methyl protons and proton H-3 experienced only a lanthanide-induced shift (LIS), $\Delta\delta$ = 0.37 and 0.53 ppm respectively. There was no evidence of $\Delta\Delta\delta$ or signal splitting. The four olefinic protons also experienced a minor $\Delta\delta$ ranging from 0.01-0.08 ppm and well-resolved multiplet peaks for protons H-8/H-9 and H-4 were observed.

The absence of enantiomeric-shift differences, $\Delta\Delta\delta$ with ketones **50**, **51**, **71** and acetate **48** demonstrated the limited utility of $[Eu(tfc)_3]$ and $[Eu(hfc)_3]$ to applications of relatively basic substrates. Functional groups give characteristic shift magnitudes[73]in the order $-NH_2$ > -OH > C=O > -O- > -CO_2R > -CN and in a preliminary study, we intended to reduce ketone **50** to the corresponding basic secondary alcohol **76**. A toluene solution of **50** under nitrogen was treated with 1.5 equiv. of diisobutylaluminum hydride at 0^0C (ice bath) and stirred at the same temperature for 2 h. After work-up and column chromatography, the corresponding alcohol **76** was isolated in 85% yield. A *dd* peak (δ_H = 4.25 ppm) for H-3 of **76** and the disappearance of the ^{13}C NMR carbonyl peak (δ_C = ~ 220 ppm) confirmed the reduction of **50** to the corresponding alcohol **76**. IR absorption ~ 3430 cm^{-1} (O-H stretching) and mass spectra further confirmed the reduction of the ketone.

The shift reagent [Eu (hfc) $_3$] was successively added to a $CDCl_3$ solution of **76** until an optimum induction of the spectra was achieved. After 5% [Eu (hfc) $_3$] mole addition, a lanthanide-induced shift (LIS), $\Delta\delta$ and enantiomeric-shift differences, $\Delta\Delta\delta$ values of 1.00 ppm and 0.18 ppm respectively were observed for one of the olefinic H-8/H-9 proton signal. The shifted ($\Delta\Delta\delta$ = 0.18 ppm) olefinic proton H-8/H-9 peaks had equal integration values as a reflection of the racemic composition of **76**. The second olefinic proton H-8/H-9 and H-3 were only shifted downfield by $\Delta\delta$ = 0.45 ppm and 1.69 ppm respectively. Further addition of the shift reagent resulted in extensive signal broadening and overlapping of olefinic peaks. Further upfield, an overall downfield shift and signal resolution was observed for all remaining signals. If

pseudocontact shifts were dependent only on covalent bonding, the proton signal splitting would have been predicted for proton H-3 of **76**. It has been known that lanthanide ions induce largely if not exclusively, pseudocontact shifts dependent only on distance and geometry, rather than contact shifts dependent on covalent bonding.[73] In this case, the geometry of **76** which brings the C_8-C_9 ethylene bridge in close proximity to the coordination site (OH group) is favoured over the distance of proton H-3 from the coordination site and consequently signal splitting was observed for H-8 or H-9 rather than for H-3. The results obtained with [Eu (tfc) $_3$] were more or less comparable with [Eu (hfc) $_3$], except for slightly poorer signal resolution.

With the large number of *ee* assay determinations envisaged, the cost and signal broadening uncertainties involved with using shift reagents encouraged the use of Mosher's acid DCC-activated esterification method to be pursued. There are few methods for determining the enantiomeric purity of chiral carbonyl compounds and it is often easier to reduce the ketone and analyse the corresponding alcohol.[70] In an attempt to establish a standard procedure, the DCC-activated esterification was first applied to the alcohols derived from racemic **50** and **51**. Ketones **50** and **51** were exclusively reduced with diisobutylaluminum hydride to the corresponding *endo*-alcohols and then derivatized with MTPA (Scheme 35).



50, R=Bu^n
51, R=Ph

78, R=Bu^n
79, R=Ph

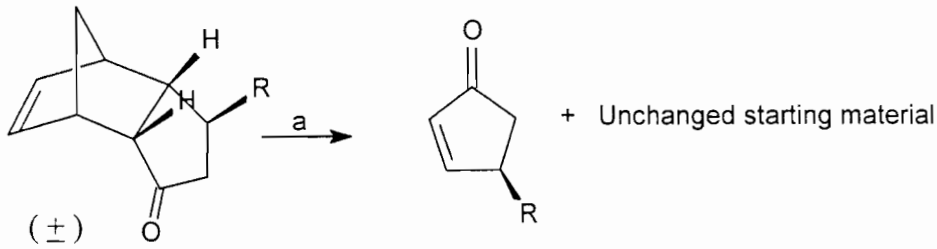
Scheme 35: a) DIBAH, toluene, 0^{0}C, 2 h a) MTPA, DCC, DIMAP, DCM, room temp, 2 h.

The *ee*-assays of the products from the chiral Lewis-acid catalysed retro-Diels-Alder reactions were accomplished as shown in Scheme 36. Analytical determinations routinely conducted on a 20 mg scale of the alcohol and 4.0

and 10.0 equiv. of MTPA and DCC respectively were used to ensure complete esterification of the alcohols and was confirmed by TLC. Addition of 3-10 mole % 4-dimethylaminopyridine accelerated esterification of MTPA with the alcohols.[72] The ^{1}H NMR spectrum of diastereoisomeric esters (**78** and **79**) revealed four *dd* (δ_H = 5.75-6.20 ppm) peaks of equal integration values corresponding to the olefinic protons H-8 and H-9 as well as a pair of 6 proton OMe *s* (δ_H = ~ 3.56 ppm) peaks. The rest of the spectrum was complicated by signal overlapping and perturbation. Usually, the ^{1}H NMR MTPA ester methoxy peaks tend to be useful when assaying *ee* composition. However, the OMe peak resonances of **78** and **79** overlapped precluding the use of these peaks to obtain the relative proportions of the diastereoisomeric composition. A slight variation of this methodology[74] was the use of shift reagent Eu(hfc)$_3$ to increase the chemical shift separation between the OMe peaks. A 5% mole addition of Eu(hfc)$_3$ to **78** or **79**, resulted in a lanthanide-induced downfield shift and a $\Delta\Delta\delta$ = 0.06 ppm increase in the chemical shift separation between the OMe peaks. The $\Delta\Delta\delta$ = 0.06 ppm increase was however not sufficient enough for the OMe peaks to be satisfactorily used for integration. The best alternative was to use the ^{19}F NMR spectrum of **78** and **79**. With a much larger chemical shift difference of the diastereotopic α-trifluoromethyl groups, it was used as our method choice for assaying diastereoisomeric composition. It is of interest to note that the OMe peaks were of marginally different intensity although racemic materials **50** and **51** were used in establishing the standard *ee* assay procedure. The inequality of the signals is a consequence of the different rate of reaction of the reagent with the enantiomers.[38] In their work with MTPA, James *et. al* reported the observation that signal difference my be quite large with hindered alcohols.[75]

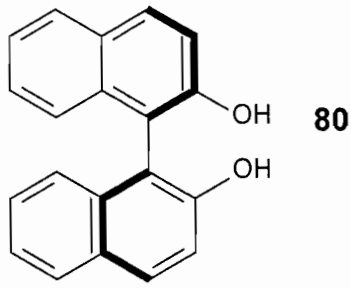
The synthesis of enantiomerically pure 4-alkyl-2-cyclopentenones **70** and **71** was attempted using the retro-Diels-Alder reactions of **50** and **51** catalysed by *in situ*-generated chiral Lewis-acids. The catalysts were generated by adding selected Lewis-acids to chiral ligands containing the diol functionality, namely BINOL (**80**) and TADDOL (**35**). The conditions under which the chiral Lewis - acids are generated such as temperature, solvent and aging time are detailed in the experimental section and a summary of these reactions is given in

Table 3 (p 50). Racemic tricyclic ketones **50** and **51** were subjected to the chiral Lewis-acid catalysed retro-Diels-Alder reactions as shown in Scheme 37. Depending on the progress of the reactions as monitored by TLC, attempts were made to stop the reactions at 50 % conversion. This was done to ensure preferential consumption of only one enantiomer. The unchanged starting material was then isolated and analysed for *ee* determination.



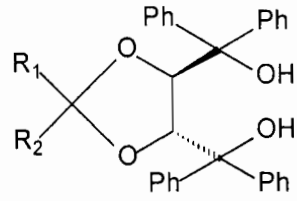
50-51 **70-71**

Scheme 36: a) Chiral Lewis acid, Maleic anhydride, DCM/DCE



BINOL

80



TADDOL

35a, R_1=R_2= Ph
35b, R_1=R_2= Me

Fig. 15

Table 3 Chiral Lewis-acid catalysed retro-Diels-Alder reactions

#	Sub.	L.acid (equiv.)	C. Ligand	T (^{0}C)	time	[c]s.m. (%)
1	**50/51**	$EtAlCl_2$ (0.2)	TADDOL-1	55	50 min	60
2	**51**	= (1.0)	=	55	30 min	55
3	**51**	= (1.1)	TADDOL-2	55	30 min	40
4	**51**	= (1.1)	=	rt	40 min	60
5	**51**	= (1.1)	TADDOL-1	0	50 min	52
6[a]	**50/51**	= (1.0)	TADDOL-2	-78-rt	15 hr	73
7[b]	**51**	Me_2AlCl (1.0)	=	0-50	2 hr	43
8[a]	**50**	$TiCl_4$ (1.2)	=	Rt	3 hr	60
9	**51**	Me_2AlCl (0.3)	BINOL	rt-45	3 hr	70
10	**51**	= (0.5)	=	rt-55	2 hr	55

Unless other wise specified 1,2-dichloroethane was used as a solvent.

[a] DCM, [b] Toluene used as solvents. [c] to avoid loss of material, recovered unchanged starting material was taken for *ee* assay.

The unchanged starting material was first reduced to the corresponding alcohol using diisobutylaluminum hydride (DIBAH) and then esterified to its Mosher's ester. The enantiomeric excess (*ee*) was then assayed from the intensity of the ^{19}F NMR chemical-shift difference of the diastereotopic α-trifluoromethyl groups of the Mosher's ester. To a solution of Mosher's acid (1.2 equiv.) in dry dichloromethane (DCM) was added the alcohol and catalytic amount of DMAP. This was followed by addition of DCC (1.6 equiv.) at 0^0C and the reaction mixture was stirred to room temperature until the alcohol was consumed. After filtration of the insoluble urea precipitate and column chromatography, the ester was submitted for ^{19}F NMR and the singlet fluorine peaks were integrated for *ee* assay.

The aldol product enone **67** (Scheme 35, p 44) was also treated with 0.5 equiv. of chiral Lewis-acid generated from TADDOL-2 and dimethylaluminum chloride (Me_2AlCl) in the presence of maleic anhydride. After stirring for 3 h at 55^0C, the reaction was quenched to give **74** and unchanged starting material **67** in 30 and 52% yield respectively. Diisobutylaluminum hydride reduction of the unchanged starting material gave the alcohol in 60%. After MTPA

esterification of the alcohol, ^{19}F NMR of the Mosher's ester of the alcohol gave two ^{19}F singlet peaks of equal integration values. The same reaction was also attempted using stoichiometric amount of the reagent at ambient (52 h reaction time) and 55 ^{0}C (3 h reaction time) temperatures but gave no evidence of enantioselectivity.

In chiral Lewis-acid catalysed Diels-Alder reactions, several factors have been ascribed to play a crucial role on the degree of asymmetric induction. These factors include the amount of catalyst, temperature as well as conformational mobility of substrate and design of catalyst. A number of titanium and aluminium chiral Lewis-acid catalysed Diels-Alder reactions reported by other workers have been conducted at low temperature ranging from - 78^{0}C up to 0^{0}C. For example, the use of stoichiometric or catalytic (in the presence of MS) Ti-TADDOLates have proved successful in the condensation of cyclopentadiene with some specific acrylamides or crotonamides. Enantiomeric excesses of 90-95% were achieved with these low-temperature reactions.[65,67] Catalytic use of 1,1'-binaphthoxydichlorotitanium has also been reported by Reetz *et al.* in the formation of a cycloadduct between methacrolein and cyclopentadiene.[65] A stoichiometric use of chiral aluminium chloride generated from $EtAlCl_2$ and chiral diols (such as BINOL) has also been applied to the Diels-Alder reaction between crotonamide and cyclopentadiene at - 78^{0}C to give a 92->98% *ee* of the adduct.[65]

In our attempted chiral Lewis-acid catalysed retro-Diels-Alder reactions (Table 3), the reactions were usually stirred to 55^{0}C to form a reasonable amount of the product. Such high temperatures might not be compatible with the performance of these *in situ*-generated chiral Lewis-acids. In addition, the low temperature and long reaction time shown in Table 3 might have resulted in the decomposition and degradation of the catalyst in use. Hence, the design of chiral catalysts, which take the effect of temperature and reaction time into consideration, needs to be addressed.

However, we were able to demonstrate the Lewis-acid catalysed retro-Diels-Alder reactions of *exo*-5-substituted tricyclodecadienones (**50-54**) and enones (**67-68**) obtained *via* the diastereoselective β-conjugate addition and aldol condensation reactions of **7** respectively. The amount of catalysts required,

temperature and conversion rate utilizing several aluminum, titanium, stannous and boron Lewis-acids were successfully investigated. In all these reactions, no double bond rearrangement or decomposition associated with highly functionalized cyclopentenones[39] was observed. This same problem has promoted chemists to include a thermal retro-Diels-Alder cleavage in their synthetic strategy toward these compounds .[70]

3. Experimental Section

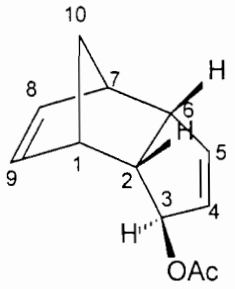
Melting points were determined using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Paragon 1000 FT-IR spectrometer.

All proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded unless otherwise specified, as deuteriochloroform solutions using tetramethylsilane as an internal standard on a Varian VXR-200 (200 MHz) or a Varian Mercury Spectrometer 300 MHz or a Varian Unity Spectrometer 400 MHz. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on the same instruments at 75 or 100 MHz using tetramethylsilane as an internal standard. ^{19}F NMR spectra of the samples were also recorded using the same instruments as deuteriochloroform solutions and tetramethylsilane as an internal standard. High-resolution mass spectrometry was performed at the mass-spectrometry unit/service of the Cape Technikon and School of Chemistry, University of the Witwatersrand using a VG70-SEQ Micromass spectrometer.

All reactions were monitored by TLC on aluminum-backed silica gel 60 F_{254} plates using an ascending technique. The plates were visualized by spraying with ceric ammonium sulfate in 8 M sulfuric acid or a 1:1 solution of 5 % *p*-anisaldehyde in ethanol and 10 % sulfuric acid in ethanol baking at 200 °C. Gravity column chromatography was done on Merck silicagel 60 (70 – 230 mesh).

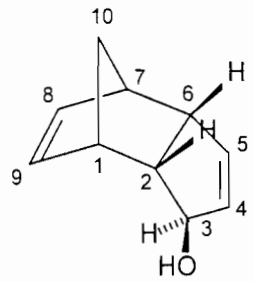
All the solvents used were dried by appropriate techniques[76,77] and all reactions except for the preparations of compounds **7**, **48** and **49** were carried out under nitrogen or argon. All reagents were purchased from the chemical suppliers except for PCC.

***Exo*-3-acetoxy-*endo*-tricyclo-[5.2.1.0^{2,6}]-deca-4,8-diene (48)**



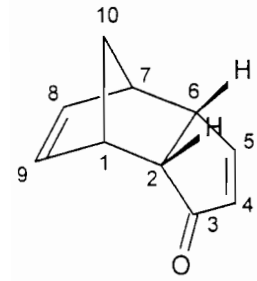
To a solution of manganese (II) acetate (10 g, 40.80 mmol) in glacial acetic acid (40 mL) was added acetic anhydride (15 mL) and the mixture was refluxed for 20 min. To this hot solution (~ 110 ^{0}C, oil bath temperature) was added potassium permanganate (1.2 g, 10.20 mmol) portion-wise and the mixture refluxed for 30 min. After cooling to 70^{0}C, dicyclopentadiene **47** (4.9 mL, 36 mmol) was added followed by potassium bromide (730 mg, 6.20 mmol) with stirring and the stirring was continued at the same temperature until the dark brown colour of Mn (IV) ion had faded (~ 1 h). After cooling, the mixture was filtered through a Celite pad, diluted with water and extracted with hexane. The extract was washed successively with 5% sodium hydrogen carbonate solution, water, brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica-gel (100g, EtOAc-hexane; 1:20) to give the acetate **48** (3.43 g, 71%) as colourless oil. IR: 1720 cm^{-1} (C=O). (Found: M$^+$, 190.0993. $C_{12}H_{14}O_2$ requires 190.0994). δ_H (300 MHz; $CDCl_3$): 6.02 (1H, *dd, J* = 5.9, 2.9 Hz, H-4), 5.90-5.83 (2H, *m*, H-8 and H-9), 5.56 (1H, *dt*, *J* = 5.9, 2.0 Hz, H-5), 4.97-4.93 (1H, *m*, H-3), 3.37 (1H, *m*, H-6), 3.12-3.07 (1H, *m*, H-1), 2.81 (1H, *ddd*, *J* = 2.0, 1.5, 1.1 Hz, H-7), 2.59 (1H, *ddd*, *J* = 2.9, 2.6, 2.2 Hz, H-2), 2.01 (3H, *s*, acetate CH_3), 1.58 (1H, *dt*, *J* = 8.4, 1.8 Hz, H-10$_a$ or H-10$_b$), 1.40 (1H, *d*, *J* = 8.4 Hz, H-10$_a$ or H-10$_b$). δ_C (75 MHz; $CDCl_3$): 21.3 (CH_3), 44.7 (CH), 44.8 (CH), 50.2 (CH), 51.3 (CH), 54.5 (C-10), 82.1 (C-3), 130.7 (C-9 or C-10), 132.5 (C-9 or C-10), 135.3 (C-5), 139.9 (C-4), 171.0 (CO).

***Exo*-3-*endo*-tricyclo-[5.2.1.0^{2,6}]-deca-4,8-dien-3-ol (49)**



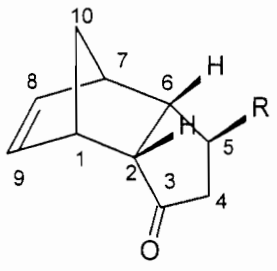
A mixture of acetate **48** (1 g, 5.25 mmol) and potassium carbonate (1.10 g, 7.87 mmol) in methanol (20 mL) was stirred at room temperature for 20 h. After evaporation of the solvent under reduced pressure, the residue was washed with water and extracted with ethyl acetate. The extract was washed with brine (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica-gel (100g, EtOAc-hexane; 1:4) to give alcohol **49** (0.71 g, 90%) as a colourless crystalline solid. m.p.: 72-73^{0}C (from hexane), (lit.[24] 71.5-72 ^{0}C). IR: 3430 (O-H stretching). (Found: M^+, 148.0889. $C_{10}H_{12}O$ requires 148.0888).δ_H(300 MHz; $CDCl_3$): 5.93 (1H, *dd*, *J* = 5.7, 3.1 Hz, H-4), 5.83 (1H, *dd*, *J* = 5.5, 2.9 Hz, H-8 or H-9), 5.77 (1H, *dt*, *J* = 5.5, 1.1 Hz, H-8 or H-9), 5.60 (1H, *dt*, *J* = 5.7, 2.0 Hz, H-5), 4.07 (1H, *br m*, H-3), 3.37 (1H, *ddd*, *J* = 2.9, 2.6, 2.2 Hz, H-6), 3.08-3.03 (1H, *br m*, H-1), 2.82-2.76 (1H, *m*, H-7), 2.53 (1H, *ddd*, *J* = 2.7, 2.2, 1.8 Hz, H-2) 1.56 (1H, *dt*, *J* = 8.1, 1.6 Hz, H-10_a or H-10_b), 1.47 (1H, *br s*, OH), 1.39 (1H, *d*, *J* = 8.1 Hz, H-10_a or 10-H_b). δ_C (75 MHz; $CDCl_3$): 44.5 (CH) 44.7 (CH), 51.1 (CH), 53.4 (CH), 54.5 (C-10), 78.9 (C-3), 132.3 (C-8 or C-9), 134.5 (C-8 or C-9), 135.3 (C-5), 137.8 (C-4).

***Endo*-tricyclo-[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (7)**

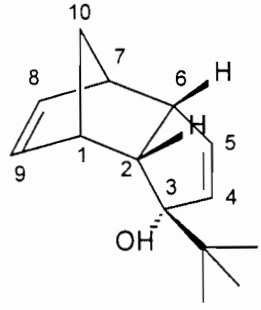


Pyridinium chlorochromate supported on alumina (8.87 g, 41.10 mmol) was added to a flask containing a solution of **49** (4.10 g, 27.43 mmol) in *n*-hexane (70 mL). After stirring overnight, the solid was removed by filtration and washed with ether (3 x 50 mL). The combined filtrate was evaporated under reduced pressure and concentrated *in vacuo*. The residue was chromatographed on silica-gel (200 g, EtOAc-hexane; 1:9), to give **7** (3.63 g, 90%) as a colourless crystalline solid. m.p.: 74-75 ^{0}C (from hexane), (lit.[24] 76^{0}C). IR: 1692 (C=O). (Found: M$^+$, 146.0737. $C_{10}H_{10}O$ requires 146.0732). δ_H (300 MHz; $CDCl_3$): 7.36 (1H, *dd*, *J* = 5.7, 2.7 Hz, H-5), 5.95-5.93 (2H, *m*, H-9 and H-8), 5.77 (1H, *dd*, *J* = 5.7, 2.9 Hz, H-4), 3.39-3.44 (1H, *m*, H-6), 3.24-3.18 (1H, br *m*, H-1), 2.98-2.93 (1H, br *m*, H-7), 2.78 (1H, *t*, *J* = 5.0 Hz, H-2), 1.75 (1H, *dt*, *J* = 8.4, 1.5, 1.2 Hz, H-10$_a$ or H-10$_b$), 1.63 (1H, *dt*, *J* = 8.4, 1.5 Hz, H-10$_a$ or H-10$_b$). δ_C (100 MHz; $CDCl_3$): 43.9 (CH), 44.9 (CH), 48.2 (CH), 50.1 (CH), 52.6 (C-10), 132.3 (C-8 or C-9), 132.5 (C-8 or C-9), 136.8 (C-4), 164.4 (C-5), 210.5 (CO).

1, 4 – Conjugate Addition Reactions



50 (R=Bu^n), **51** (R=Ph), **52** (R=Me), **53** (R=Et), **54** (R=Bu^t)



55

***Exo*-5-*n*-Butyl-*endo*-tricyclo-[5.2.1.0^{2,6}]-dec-8-en-3-one (50)**

A solution of *n*-butyllithium (4.30 mL of a 1.6 M solution in hexane, 6.90 mmol) was added gradually to a suspension of copper (I) iodide (676 mg, 3.60 mmol) in dry ether at - 5^{0}C. After stirring for 15 min at - 5 ^{0}C, the mixture was cooled to - 78^{0}C and a solution of **7** (250 mg, 1.70 mmol) in ether (10 mL) was added slowly. The reaction mixture was stirred at - 78^{0}C for 1 h and then quenched

with a saturated aqueous ammonium chloride solution. The product was extracted with ether (2 x 10 mL) and the combined organic filtrates washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was chromatographed on silica-gel (EtOAc-hexane; 1:20) to give **50** (320 mg, 92%) as a colourless oil. IR: 1724 cm^{-1}(C=O). (Found: M^+, 204.1517. $C_{14}H_{20}O$ requires 204.1514). δ_H (400 MHz; $CDCl_3$): 6.14 (2H, *m*, H-8 and H-9), 3.15 (1H, *m*, H-1), 3.03-3.01 (1H, *m*, H-7), 2.92 (1H, *ddd*, *J* = 9.5, 4.6, 1.8 Hz, H-2), 2.62 (1H, *dt*, *J* = 9.5, 4.1 Hz, H-6), 2.19 (1H, *dd*, *J* = 18.5, 8.9 Hz, H-4_{endo}), 1.90 (1H, *ddd*, 18.5, 8.9, 1.8 Hz, H-4_{exo}), 1.71-1.64 (1H, *m*, H-5), 1.55 (1H, *d*, *J* = 6.8 Hz, H-10_a), 1.42 (1H, *d*, *J* = 6.8 Hz, H-10_b), 1.34-1.25 (6H, *m*, -($\mathbf{CH_2}$)$_3$$CH_3$), 0.91 (3H, *t*, *J* = 6.8 Hz, -CH_3). δ_C (75 MHz; $CDCl_3$): 14.0 (CH_3), 22.7 (CH_2), 29.7 (CH_2), 36.8 (CH_2), 37.7 (CH_2), 46.1 (CH), 47.2 (CH), 48.3 (CH), 48.8 (CH), 52.3 (CH), 54.8 (C-10), 135.3 (C-8 or C-9), 136.1 (C-8 or C-9), 220.9 (CO).

Exo-5-Phenyl-_endo_-tricyclo-[5.2.1.$0^{2,6}$]-dec-8-en-3-one (51)

A solution of phenyllithium (4.0 mL of a 1.8 M solution in hexane, 7.20 mmol) was added gradually to a suspension of copper (I) iodide (412 mg, 2.20 mmol) in dry ether at 0^0C. The mixture was stirred at 0^0C for 15 min. This was followed by slow addition of **7** (201 mg, 1.40 mmol) in ether (10 mL). The reaction mixture was stirred at room temperature for 2 h and then quenched with a saturated aqueous ammonium chloride solution. The aqueous phase was extracted with ether (2 x 20 mL) and the combined organic phases washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The dark yellow oil residue was chromatographed on silica-gel (20 g, EtOAc-hexane; 1:20) to give **51** (298 mg, 95%) as a slightly-yellow oil. IR: 1728 cm^{-1} (C=O), 772 cm^{-1} (aromatic C-H). (Found: M^+, 224.1188. $C_{16}H_{16}O$ requires 224.1201). δ_H (400 MHz; $CDCl_3$): 7.32 (2H, *t*, *J* = 7.7 Hz, H*m*), 7.21 (1H, *t*, *J* = 7.5 Hz, H*p*), 7.16 (2H, *d*, *J* = 7.6 Hz, H*o*) 6.29 (1H, *dd*, *J* = 5.6, 3.0 Hz, H-8 or H-9), 6.26 (1H, *dd*, *J* = 5.6, 2.9 Hz, H-8 or H-9), 3.24 (1H, *m*, H-1), 3.15 (1H, *m*, H-7), 3.13 (1H, *ddd*, *J* = 9.6, 4.6, 1.7 Hz, H-2), 3.02 (1H, *dt*, *J* = 9.6, 4.4 Hz, H-6), 2.92 (1H, *m*, H-5), 2.52 (1H, *dd*, *J* = 18.3, 8.9 Hz, H-4_{endo}),

2.43 (1H, *ddd*, *J* = 18.3, 7.9, 1.7 Hz, H-4_{exo}), 1.61 (1H, *d*, *J* = 8.3 Hz, H-10_a or H-10_b), 1.44 (1H, *d*, *J* = 8.3 Hz, H-10_a or H-10_b). δ_C (100 MHz; $CDCl_3$): 42.7 (CH_2), 46.2 (CH), 46.9 (CH), 49.4 (CH), 51.1 (CH), 52.4 (CH), 55.0 (C10), 126.2 (C-ar.), 126.6 (2xC-ar.), 128.7 (2xC ar.), 134.9 (C-8 or C-9), 136.7(C-8 or C-9), 146.8 (C-ar.), 219.4 (CO).

Exo-5-Methyl-_endo_-tricyclo-[5.2.1.$0^{2,6}$]-dec-8-en-3-one (52)

A solution of methyllithium (11.50 mL of a 1.4 M solution in ether, 16.1 mmol) was added gradually to a suspension of copper (I) iodide (1.5 g, 7.87 mmol) in dry ether and stirred for 15 min at - 5^0C. To this mixture was then added gradually at - 78^0C a solution of enone **7** (0.455 g, 3.10 mmol) in ether (10 mL) .The reaction mixture was stirred at room temperature for 1 h and then a saturated aqueous ammonium chloride solution was added. The aqueous phase was extracted with ether and the combined organic solutions washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was chromatographed on silica-gel (40 g, EtOAc-hexane; 1:9) to give **52** (455 mg, 90%) as colourless oil. IR: 1724 cm^{-1} (C=O). (Found: M^+, 162.1039. $C_{11}H_{14}O$ requires 162.1045). δ_H (300 MHz; $CDCl_3$): 6.14 (1H, *dd*, *J* = 5.4, 3.1 Hz, H-8 or H-9), 6.07 (1H, *dd*, *J* = 5.4, 2.9 Hz, H-8 or H-9), 3.17 (1H, *m*, H-1), 3.06 (1H, *m,* H-7), 2.92 (1H, *ddd*, *J* = 9.5, 4.7, 1.7 Hz, H-2), 2.52 (1H, *dt*, *J* = 9.5, 3.8 Hz, H-6), 2.21 (1H, *dd,* *J* = 20.1, 10.6 Hz, H-4_{endo}), 1.89-1.83 (2H, *m*, H-4_{exo} and H-5), 1.52 (1H, *d*, *J* = 8.2 Hz, H-10_a or H-10_b), 1.36 (1H, *d*, *J* = 8.2 Hz, H-10_a or H-10_b), 1.09 (3H, *d*, *J* = 6.8 Hz, CH_3). δ_C (75 MHz; $CDCl_3$): 23.4 (CH_3), 31.2 (CH_2), 46.4(CH), 46.7 (CH), 49.7 (C-H), 50.5 (C-H), 52.3 (CH), 54.7 (C-10), 135.1 (C-8 or C-9), 136.0 (C-8 or C-9), 221.1 (CO).

Exo-5-Ethyl-_endo_-tricyclo-[5.2.1.$0^{2,6}$]-dec-8-en-3-one (53)

Bromoethane (0.3 mL, 4.00 mmol) was added gradually to magnesium turnings (78.3 mg, 3.22 mmol) in dry ether (10 mL) and the mixture was stirred until the magnesium had been consumed. To the turbid mixture was

added dry CuI (20 mg, 0.11 mmol) and the resulting green-yellow mixture stirred at 0^0C for 30 minutes. The mixture was cooled to - 78^0C and a solution of enone **7** (100 mg, 0.68 mmol) in ether (10 mL) was added drop wise over a period of 5 min. After stirring for 1 h at - 78^0C, the reaction mixture was quenched with a saturated aqueous ammonium chloride solution. The aqueous phase was extracted with ether and the combined organic phase washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. Column chromatography on silica-gel (10 g, EtOAc-hexane; 1:10) gave **53** (96.5 mg, 80%) as a colourless oil. IR 1725 cm^{-1} (C=O). (Found: M^+, 176.1201. $C_{12}H_{16}O$ requires 176.1201). δ_H (300 MHz; $CDCl_3$): 6.13 (2H, *m*, H-8 and H-9), 3.18-3.12 (1H, *m*, H-1), 3.04-2.98 (1H, *m,* H-7), 2.90 (1H, *ddd*, *J* = 9.5, 4.4, 1.8 Hz, H-2), 2.60 (1H, *dt*, *J* = 9.5, 4.0 Hz, H-6), 2.18 (1H, *dd, J* = 18.7, 9.5 Hz, H-4_{endo}), 1.91 (1H, *ddd*, *J* = 18.7, 6.6, 1.8 Hz H-4_{exo}), 1.66-1.56 (1H, *m*, H-5), 1.53 (1H, *d*, *J* = 8.4 Hz, H-10_a or H-10_b), 1.46-1.55 (2H, *m*, CH_2), 1.40 (1H, *d*, *J* = 8.75 Hz, H-10_a or H-10_b), 0.94-0.86 (3H, *t*, *J* = 7.32 Hz, CH_3). δ_C (75 MHz; $CDCl_3$): 11.9 (CH_3), 30.5 (CH_2), 38.5 (CH_2), 46.2 (CH), 47.2 (CH), 47.9 (CH), 48.5 (CH), 52.3 (CH), 54.9 (C-10), 135.2 (C-8 or C-9), 136.0 (C-8 or C-9), 220.9 (CO).

***Exo*-5-*t* -Butyl-*endo*-tricyclo-[5.2.1.$0^{2,6}$]-dec-8-en-3-one (54)**

A solution of *t*-butyllithium (6.50 mL of a 1.7 M solution in pentane, 11.05 mmol) was added gradually to a suspension of copper (I) iodide (1.1 g, 5.48 mmol) in dry ether at - 5^0C. After stirring for 15 min, the mixture was cooled to - 78^0C and a solution of **7** (200 mg, 1.37 mmol) in ether (10 mL) was added slowly. The reaction mixture was stirred for 1 h at - 78^0C and then quenched with a saturated aqueous ammonium chloride solution. The product was extracted with ether (2 x 10 mL) and the combined organic filtrates washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was chromatographed on silica-gel (EtOAc-hexane; 1:20) to give **54** (117.5 mg, 42%) and the 1,2-addition product **55** (42.4 mg, 15%) as colourless oils. **54**: IR: 1718 cm^{-1}(C=O). (Found: M^+, 204.1531. $C_{14}H_{20}O$ requires 204.1514). δ_H (400 MHz; $CDCl_3$): 6.14 (2H, *m*, H-8 and H-9),

3.13 (1H, *m*, H-1), 2.97-2.91 (1H, *m*, H-7), 2.87 (1H, *dd*, *J* = 9.9, 4.6 Hz, H-2), 2.75 (1H, *dt*, *J* = 9.9, 4.9 Hz, H-6), 2.12 (1H, *ddd*, *J* = 18.7, 8.4, 1.8 Hz, H-4_{exo}), 2.03 (1H, *dd*, 18.7, 9.3 Hz, H-4_{endo}), 1.54 (1H, *dt*, *J* = 8.4 1.8 Hz, H-10_a), 1.51-1.46 (1H, *m*, H-5), 1.43 (1H, *dt*, *J* = 6.8, 1.5 Hz, H-10_b), 0.86 (9H, *d*, *J* = 1.8 Hz, $(CH_3)_3$). δ_C(75 MHz; $CDCl_3$): 27.1 ($(CH_3)_3$), 33.2 (C-11), 43.9 (CH_2), 44.0 (CH), 46.0 (CH), 48.1 (CH) 48.2 (CH), 52.4 (CH), 55.6 (C-10),135.2 (C-8 or C-9), 136.1 (C-8 or C-9), 220.9 (CO). **55:** IR: 3520 cm^{-1}(OH). (Found: M^+, 204.1519. $C_{14}H_{20}O$ requires 204.1514). δ_H(400 MHz; $CDCl_3$): 6.17 (1H, *dd*, *J* = 5.6, 1.9 Hz, H-4), 5.83 (1H, *dd*, *J* = 5.6, 3.2 Hz, H-5), 5.56 (1H, *dd*, *J* = 5.7, 1.9 Hz, H-8 or H-9), 5.50 (1H, *dd*, *J* = 5.7, 1.6 Hz, H-8 or H-9), 3.19-3.14 (1H, *m*, H-6), 2.84-2.88 (1H, *m*, H-2), 2.84 (2H, *m*, H-1 and H-7), 1.58 (1H, *d*, *J* = 8.0 MHz, H-10_a or H-10_b), 1.47 (1H, *d*, *J* = 8.0 Hz, H-10_a or H-10_b), 1.27 (1H, *bs*, OH), 0.92 (9H, *s*, $(CH_3)_3$). δ_C (100 MHz; $CDCl_3$): 25.1 ($(CH_3)_3$), 38.1 (C-11), 46.1 (CH), 46.7 (CH), 49.2 (CH), 52.9 (CH), 54.4 (C-10), 88.3 (C-3), 133.8 (C-8 or C-9), 135.3 (C-8 or C-9), 135.8 (C-4), 136.2 (C-5).

1, 4-Addition of Triorganozincate $Bu^t_3ZnLi{\cdot}2LiCl$

A saturated solution of zinc chloride (0.83 mmol) in THF was treated with *t*-butyllithium (1.50 mL of a 1.7 M solution in pentane, 2.55 mmol) and stirred for 30 min at 0^0C. The temperature was lowered to - 70^0C and a THF (5 mL) solution of **7** (100 mg, 0.68 mmol) was added slowly. The reaction mixture was stirred at the same temperature for 1 h and then quenched with a saturated aqueous ammonium chloride solution. The product was extracted with ether (2 x 10 mL) and the combined organic filtrates washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was chromatographed on silica-gel (EtOAc-hexane; 1:20) to give **54** (75 mg, 54%) as a colourless oil. The starting material was recovered in 7.5%.

Attempted kinetic-enolate alkylations (alkylations at C4)

Using diisopropylamide (LDA)

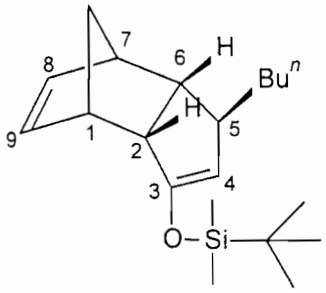
A solution of lithium diisopropylamide in THF was prepared by addition of *n*-butyllithium (0.80 mL of 1.6 M in hexane, 1.28 mmol) to diisopropylamine (0.2 mL, 1.55 mmol) in THF (5 mL) at - 78^{0}C followed by stirring for 30 min at - 78^{0}C, and for another 30 min at 0^{0}C. The solution was cooled to - 78^{0}C and **50** (200 mg, 1.00 mmol) in THF (1.5 ml) was added slowly with stirring, and the reaction mixture was maintained at - 78^{0}C for 30 min before rapid addition of ethyl bromide (0.70 mL, 9.46 mmol). Following the alkylhalide addition, the reaction mixture was stirred at - 78^{0}C for 1 h, and allowed to warm slowly to room temperature. After being stirred at room temperature for 48 h, the reaction mixture was treated with aqueous ammonium chloride solution and the product extracted with ether (2 x 15 mL). The combined organic filtrates were washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was chromatographed on silica-gel (EtOAc-hexane; 1:20) to give the starting material **50** (160 mg, 80 %) as the sole product isolated.

Using Bu^n_2CuLi

A solution of *n*-butyllithium (3.50 mL of a 1.6 M solution in hexane, 5.60 mmol) was added gradually to a suspension of copper (I) iodide (550 mg, 2.90 mmol) in dry ether at 0^{0}C. The mixture was stirred at 0^{0}C for 15 min and a solution of **7** (200 mg, 1.37 mmol) in ether (10 mL) was added slowly. After a 2 h room temperature stirring, allyl chloride (12.37 mmol) was added and stirring was continued for 2 h. The reaction mixture was then quenched with a saturated aqueous ammonium chloride solution, the product extracted with ether (2 x 10 mL) and the combined organic filtrates washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was chromatographed on silica-gel (25 g, EtOAc-hexane; 1:20) to give the 1, 4-conjugate addition product **50** (225 mg, 80 %) as the sole product.

Kinetic-enolate trapping using TBDMSCl

3-*t*-Butyldimethylsilyloxytricyclo-[5.2.1.$0^{2,6}$]-deca-3,8-diene (65):



A solution of lithium diisopropylamide in THF was prepared by addition of *n*-butyllithium (1.3 mL of 1.6 M in hexane, 2.08 mmol) to diisopropylamine (0.3 mL, 2.20 mmol) in THF (4 mL) at -78^{0}C followed by stirring at - 78^{0}C for 1 h. A solution of **50** (200 mg, 1.00 mmol) in THF (3 mL) was then added slowly and stirred for 30 min at -78^{0}C before the rapid addition of *t*-butyldimethylsilylchloride (370 mg, 2.50 mmol). The reaction mixture was then allowed to warm slowly to room temperature. After stirring for 12 h at room temperature, the reaction mixture was treated with a saturated aqueous sodium hydrogen carbonate solution and the product isolated by extraction with ether. The extracts were dried (Na_2SO_4), and the solvent evaporated under reduced pressure and concentrated in *vacuo*. The residue was chromatographed on silica-gel (20 g, hexane) to give silyl enol ether **65** as a colourless oil (160 mg, 50 %). IR: 1013 cm^{-1} (O-Si); (Found: M$^+$, 318.2360. $C_{20}H_{34}OSi$ requires 318.2380);δ_H (400 MHz; $CDCl_3$) 6.03-5.99 (2H, *m*, H-8 and H-9), 4.34 (1H, *m*, H-4), 3.00-2.93 (1H, *m*, H-2), 2.90-2.85 (1H, *m*, H-1), 2.84-2.79 (1H, *m*, H-7), 2.25-2.17 (1H, *m*, H-6), 1.83-1.73 (1H,*m*, H-5), 1.49 (1H, *dt*, *J* = 8.0, 1.7 Hz, H-10$_a$ or H-10$_b$), 1.35-1.25 (6H, *m*, $(CH_2)_3$), 1.23 (1H, *d*, *J* = 8.0 Hz, H-10$_a$ or H-10$_b$), 0.95-0.85 (12H, *m*, 4 (CH_3)), 0.14(3H, *s*, Si-CH_3), 0.12(3H, *s*, Si-CH_3); δ_C (100 MHz; $CDCl_3$) - 4.8 (Si-$(CH_3)_2$), 14.1 (CH_3), 18.1 (Si-**C**$(CH_3)_3$), 22.9 (CH_2), 25.9 ($(CH_3)_3$), 30.0 (CH_2), 38.1 (CH_2), 44.1 (CH), 44.2 (CH), 46.4 (CH), 47.2 (CH), 50.2 (CH), 53.4 (C-10), 108.2 (C-4), 133.7 (C-8 or C-9), 135.5 (C-8 or C-9), 155.4 (C-3).

Alkylation of silyl enol ether 65

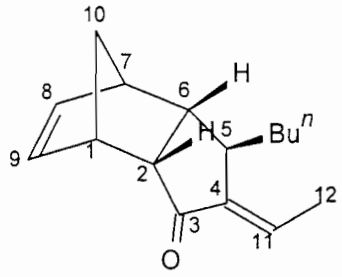
Using tetra-*n*-butylammonium fluoride (TBAF)

Tetra-*n*-butylammonium fluoride (1 M in THF, 0.7 ml, 0.70 mmol) and 4Å molecular sieves were suspended in freshly-distilled THF (3 ml) and stirred for 12 h. The flask was cooled to - 78^{0}C and a THF solution of silyl enol ether **65** (200 mg, 0.63 mmol) and benzyl bromide (0.3 ml, 2.52 mmol) was transferred to the tetra-*n*-butylammonium fluoride suspension. After stirring for 30 min at - 78^{0}C and 5 h at room temperature, the reaction mixture was diluted with hexane, filtered through celite and the solvent evaporated under reduced pressure. The slightly yellow residue was chromatographed on silica (EtOAc-hexane; 1:20) to give the parent ketone (**50**) (116 mg, 90 %) as the only product.

Using titanium tetrachloride ($TiCl_4$)

Benzyl bromide (0.08 ml, 0.64 mmol) was first added to a solution of silyl enol ether **65** (50 mg, 0.16 mmol) in dry dichloromethane (3 mL). The mixture was cooled to - 78 ^{0}C, treated with titanium tetrachloride (0.2 mL, 0.2 mmol) and stirred for 3 h at - 78^{0}C. The reddish brown reaction mixture was then poured rapidly into ice-water and shaken vigorously with dichloromethane in a separatory funnel. The combined organic phases were dried ($MgSO_4$), the solvent evaporated under reduced pressure and concentrated in *vacuo*. The residue was chromatographed on silica (EtOAc-hexane; 1:20) to give the parent ketone (**50**) as the only product (30 mg, 92 %).

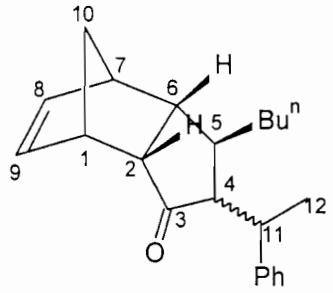
***Exo*-5-*n*-Butyl-4*E*-ethylidene-*endo*-tricyclo-[5.2.1.$0^{2,6}$]-dec-8-en-3-one (**67**):**



A solution of *n*-butyl bromide (0.40 mL, 3.70 mmol) was added gradually to magnesium turnings (94 mg, 3.85 mmol) in dry ether (10 mL) and the mixture was stirred until the magnesium had been consumed. Dry CuI (16 mg, 85.20 mmol) was then added to the turbid Grignard reagent and the mixture was stirred at -5^{0}C for 15 min. A solution of **7** (400 mg, 2.75 mmol) in ether was added to the mixture and stirred at 0^{0}C for 2 h. The reaction mixture was cooled to - 15^{0}C and acetaldehyde (16 ml, 285 mmol) was added gradually over a period of 15 min. Once the addition was complete, stirring was continued for 1 h at -15^{0}C and then for 30 min at 0^{0}C. The reaction mixture was hydrolysed with a solution of hydrogen chloride (2N) at 0^{0}C and the product extracted with ether. The combined organic extract was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and the solvent evaporated under reduced pressure and concentrated in *vacuo*. The crude product was dissolved in benzene (20 mL) and refluxed for 1 h using a Dean-Stark apparatus in the presence of a catalytic amount of *p*-toluenesulfonic acid. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution, the organic phase extracted with ethyl acetate and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue chromatographed on silica-gel (50g, EtOAc-hexane; 1: 25) to give **67** (475 mg, 75% overall) as a slightly yellow oil. IR: 1711 (C=O). (Found: M^+, 230.1665. $C_{16}H_{22}O$ requires 230.1671). δ_H (300 MHz; $CDCl_3$): 6.36 (1H, *qd*, *J* = 7.3, 2.2 Hz, H-11), 5.97 (1H, *dd*, *J* = 5.5, 2.9 Hz, H-8 or H-9), 5.92 (1H, *dd*, *J* = 5.5, 2.7 Hz, H-8 or H-9), 3.24-3.18 (1H, *m*, H-1), 3.03-2.98 (1H, *m*, H-7), 2.95 (1H, *dd*, *J* = 8.8, 4.8 Hz, H-2), 2.51 (1H, *ddd*, *J* = 8.8, 4.0, 1.8 Hz, H-6), 2.44-2.36 (1H, br *m*, H-5), 1.72 (3H, *dd*, *J* = 7.3, 1.1 Hz, $^{12}CH_3$), 1.48 (1H, *dt*, *J*

= 8.0, 1.8 Hz, H-10_a or H-10_b), 1.39 (1H, *dt*, *J* = 8.0, 1.5 Hz, H-10_a or H-10_b), 1.37-1.24 (6H, *m*, -C_3H_6), 0.94-0.86 (3H, *m*, CH_3). δ_C (75 MHz; $CDCl_3$): 14.1(CH_3), 14.9 (CH_3), 22.8 (CH_2), 29.1 (CH_2), 35.8 (CH_2), 40.3 (CH), 44.3 (CH), 47.4 (CH), 47.4 (CH), 51.5 (CH), 53.8 (C-10), 131.5 (C-4), 133.4 (C-8 or C-9), 135,9 (C-8 or C-9), 145.7 (C-11), 208.9 (CO).

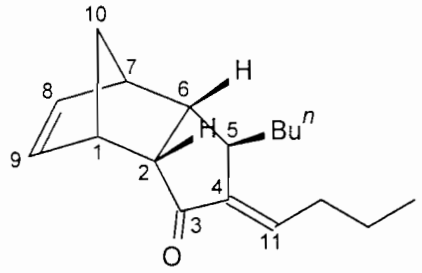
***Exo*-5-*n*-Butyl-4-(1-phenethyl)-*endo*-tricyclo-[5.2.1.$0^{2,6}$]-dec-8-en-3-one (69):**



A solution of phenyllithium (1.00 mL, 3.61 mmol in hexane) was added gradually to a suspension of copper (I) iodide (355 mg, 1.87 mmol) in dry ether (5 mL) at 0^0C. The mixture was stirred for 15 min and a solution of **67** (213 mg, 0.93 mmol) in ether (10 mL) was added slowly. The reaction mixture was stirred at room temperature for 2 h and quenched with a saturated aqueous ammonium chloride solution. The product was extracted with ether (2 x 10 mL) and the combined organic filtrate washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (20 g, EtOAc-hexane; 1:20) to give **69** (200mg, 70 %) as a colourless crystalline solid. m.p.: 60^0C (from hexane). IR: 1723 (C=O), 770 cm^{-1} (aromatic C-H), (Found: M^+, 308.2132. $C_{22}H_{28}O$ requires 308.2140);δ_H (400 MHz; $CDCl_3$) 7.27-7.11 (5H, *m*, aromatic), 5.90 (1H, *dd*, *J* = 5.5, 2.9 Hz, H-8 or H-9), 5.82 (1H, *dd*, *J* = 5.5, 3.0 Hz, H-8 or H-9), 3.29 (1H, *qd*, *J* = 7.3, 3.7 Hz, H-11), 3.18-3.12 (1H, *m*, H-1), 2.96 (1H, *ddd*, *J* = 10.2, 4.4, 2.6 Hz, H-2), 2.95-2.90 (1H, *m*, H-7), 2.46 (1H, *ddd*, *J* = 10.2, 4.02, 2.2 Hz, H-6), 2.30 (1H, *dt*, *J* = 11.43, 3.1 Hz, H-4), 1.53 (1H, *d*, *J* = 8.4 Hz, H-10_a or H-10_b), 1.40 (1H, *d*, *J* = 8.4 Hz, H-10a or H-10_b), 1.24 (3H, *d*, *J* = 7.32 Hz, $PhCCH_3$), 1.20-1.15 (1H, *m*, H-5), 1.1-1.9 (6H, br *m*, $(\mathbf{CH_2})_3CH_3$), 0.86-0.78 (3H, *t*, $(CH_2)_3\mathbf{CH_3}$); δ_C(75 MHz; $CDCl_3$) 14.0 (CH_3), 15.8 (CH_3), 22.6 (CH_2), 29.6 (CH_2), 36.4 (CH_2), 37.1 (CH), 39.4 (CH), 44.9 (CH), 46.3 (CH),

47.5 (CH), 52.5 (CH), 54.9 (C-10), 64.9 (C-11), 125.9 (C-ar.), 127.9 (2xC-ar.), 127.9 (2xC-ar.), 135.3 (C-8 or C-9), 136.9 (C-8 or C-9), 144.9 (C-ar.), 218.8 (CO).

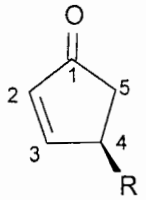
Exo-5-_n_-Butyl-4-butylidene -_endo_-tricyclo [5.2.1.$0^{2,6}$] dec-8-en-3-one (68)



A solution of *n*-butyl bromide (0.3 mL, 2.74 mmol) was added gradually to magnesium turnings (50 mg, 2.05 mmol) in dry ether (10 mL) and was stirred until the magnesium had been consumed. Dry CuI (10 mg, 53.25 mmol) was then added to the turbid Grignard reagent and the mixture was stirred for 15 min at - 5^0C. A solution of **7** (150 mg, 1.03 mmol) in ether was added to the mixture and stirred for 2 h at 0^0C. The reaction mixture was then cooled to - 15^0C and *n*-butanal (0.56 mL, 6.20 mmol) was added gradually over a period of 10 min. Once the addition was complete, stirring was continued for 1 h at - 15^0C and then for 30 min at 0^0C. The reaction mixture was hydrolysed with hydrogen chloride solution (2N) at 0^0C, the product extracted with ether and the organic extract washed with saturated aqueous sodium chloride solution and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and concentrated in *vacuo*. The crude product was dissolved in benzene (20 mL) and refluxed for 1 h using a Dean-Stark apparatus in the presence of a catalytic amount of *p*-toluenesulfonic acid. The reaction was then quenched with saturated aqueous sodium hydrogen carbonate solution, the organic phase extracted with ethyl acetate and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue chromatographed on silica gel (30g, EtOAc-hexane; 1: 25) to give **68** (168 mg, 64% overall) as a slightly yellow oil. IR: 1713 (C=O). (Found: M^+, 258.1982. $C_{18}H_{26}O$ requires 258.1984). δ_H (300 MHz; $CDCl_3$): 6.27 (1H, *t*, *J* = 7.6, 2.3 Hz, H-11), 5.96-5.88 (2H, *m*, H-8 and H-9), 3.2 (1H, *m*, H-1), 2.99 (1H, *m*, H-7), 2.94 (1H, *dd*, *J* = 8.8, 4.8 Hz, H-2), 2.50 (1H, *ddd*, *J* = 8.8, 4.0, 1.8 Hz, H-6), 2.41-2.31 (1H, br

m, H-5), 2.11-1.92 (2H, *m*, $^{12}CH_2$), 1.50 (1H, *dt*, *J* = 8.0, 1.8 Hz, H-10_a or H-10_b), 1.45 (1H, *dt*, *J* = 8.0, 1.5 Hz, H-10_a or H-10_b), 1.38-1.22 (8H, *m*), 0.90 (6H, *t*, *J* = 7.32 Hz, 2xCH_3). δ_C (100 MHz; $CDCl_3$): 13.9 (CH_3), 14.0 (CH_3), 21.9 (CH_2), 22.8 (CH_2), 28.9 (CH_2), 31.2 (CH_2), 36.4 (CH_2), 40.5 (CH), 44.2 (CH), 47.4 (CH), 47.5 (CH), 51.5 (C-5), 53.8 (C-10), 133.5 (C-4), 135.8 (C-8 or C-9), 136.8 (C-8 or C-9), 144.8 (C-11), 209.3 (CO).

The Retro-Diels-Alder Reactions



70 (R=Bu^n), **71** (Ph), **72** (Me), **73**(Et)

4-Butylcyclopent-2-enone (**70**):

A solution of **50** (200 mg, 0.98 mmol) and maleic anhydride (0.15 g, 1.47 mmol) in 1,2-dichloroethane (10 mL) was treated with ethylaluminum dichloride (1.1 mL of a 1.0 M solution in hexane) at ambient temperature. The solution was then stirred at 55^{0}C for 1.5 h, cooled to room temperature and quenched with a saturated aqueous sodium hydrogen carbonate solution. The product was isolated by extraction with ether and the combined organic extract dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified on silica-gel (10 g, EtOAc-hexane; 1:20) to give **70** (108 mg, 80%) as a slightly yellow oil. IR: 1750 cm^{-1} (C=O). (Found: M$^+$, 138.1035. $C_9H_{14}O$ requires 138.1045). δ_H (300 MHz, $CDCl_3$): 7.64 (1H, *dd*, *J* = 5.8, 2.5 Hz, H-3), 6.14 (1H, *dd*, *J* = 5.8, 2.0 Hz, H-2), 2.94 – 2.83 (1H, *m*, H-4), 2.53 (1H, *dd*, *J* = 18.7, 6.4 Hz, H-5_a), 1.96 (1H, *dd*, *J* = 18.7, 2.2 Hz, H-5_b), 1.7-1.2 (6H, *m*, 3 x (CH_2)), 0.91 (3H, br. *t*, *J* = 6.5, CH_3). δ_C (75 MHz; $CDCl_3$): 13.8 (CH_3), 22.6 (CH_2), 29.7 (CH_2), 34.4 (CH_2), 40.9 (C5), 41.4 (C4), 133.5 (C2), 168.5 (C3), 209.9 (CO).

4-Phenylcyclopent-2-enone (**71**):

A solution of **51** (150 mg, 0.67 mmol) and maleic anhydride (0.33 g, 3.35 mmol) in 1,2-dichloroethane (5.40 mL) was treated with ethylaluminum dichloride (0.8 mL of a 1.0 M solution in hexanes) at ambient temperature. The solution was then stirred at 55^{0}C for 1.5 h, cooled to room temperature and quenched with a saturated aqueous sodium hydrogen carbonate solution. The product was isolated by extraction with ether and the combined organic extracts dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the yellow residue purified on silica gel (20 g, EtOAc-hexane; 1:10) to give **71** (96 mg, 81 %) as slightly yellow oil. IR: 1745 cm^{-1} (C=O). (Found: M^+, 158.0722. $C_{11}H_{10}O$ requires 158.0731). δ_H (400 MHz, $CDCl_3$): δ 7.71 (1H, *dd*, *J* = 5.6, 2.5 Hz, H-3), 7.34 (2H, *t*, *J* = 7.5 Hz, H_m), 7.27 (1H, *t*, *J* = 7.5 Hz, H_p), 7.15 (2H, *d*, *J* = 6.8 Hz, H_o), 6.35 (1H, *dd*, *J* = 5.6, 2.1 Hz, H-2), 4.18 (1H, *dq*, *J* = 6.8, 2.4, 2.1 Hz, H-4), 2.90 (1H, *dd*, *J* = 18.9, 6.8 Hz, H-5_a), 2.35 (1H, dd, *J* = 18.9, 2.4 Hz, H-5_b). δ_C (100 MHz, $CDCl_3$): 43.9 (C-5), 46.7 (C-4), 127.0 (C-ar.), 127.2 (2xC-ar.), 128.9 (2xC-ar.), 133.9 (C-ar.), 141.4 (C-2), 166.4 (C-3), 209.6 (CO).

4-Methylcyclopent-2-enone (**72**):

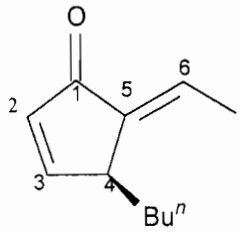
A solution of **52** (125 mg, 0.76 mmol) and maleic anhydride (0.40 g, 4.05 mmol) in 1,2-dichloroethane (5.40 mL), was treated with ethylaluminum dichloride (0.8 mL of a 1.0 M solution in hexane) at ambient temperature. The reaction was stirred at 55^{0}C for 1.5 h, cooled to room temperature and quenched with a saturated aqueous sodium hydrogen carbonate solution. The product was isolated by extraction with ether and the combined organic extract dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue purified on silica-gel (15g, EtOAc-hexane; 1:9) to give **72** (44 mg, 50%) as a colourless oil. IR: 1760 cm^{-1} (C=O). (Found: M^+, 96.0570. C_6H_8O requires 96.0575).δ_H (400 MHz, $CDCl_3$): δ 7.53 (1H, *dd*, *J* = 5.3, 2.5 Hz, H-3); 6.08 (1H, *dd*, *J* = 5.3, 1.9 Hz, H-2), 3.17 - 2.77 (1H, br. *m*, H-4); 2.59

(1H, *dd*, *J* = 16.9, 6.5 Hz, H-5_a); 1.86 (1H, *dd*, *J* = 16.9, 2.0 Hz, H-5_b); 1.25 (3H, *d*, *J* = 7.0 Hz, CH_3). δ_C (100 MHz; $CDCl_3$): 19.3 (CH_3), 26.8 (C-4), 52.4 (C-5), 125.6 (C-2), 146.7 (C-3), 197.6 (CO).

4-Ethylcyclopent-2-enone (**73**):

A solution of **53** (200 mg, 1.14 mmol) and maleic anhydride (0.25 g, 2.53 mmol) in 1,2-dichloroethane (5.40 mL) was treated with ethylaluminum dichloride (1.3 ml of a 1.0 M solution in hexane) at ambient temperature. The solution was stirred at 55^0C for 1.5 h, cooled to room temperature and quenched with a saturated aqueous sodium hydrogen carbonate solution. The product was isolated by extraction with ether and the combined organic extract dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified on silica-gel (15g, EtOAc-hexane; 1:9) to give **73** (87.5 mg, 60%) as colourless oil. IR: 1740 cm^{-1} (C=O). (Found: M^+, 110.0729. $C_7H_{10}O$ requires 110.0732). δ_H (400 MHz, $CDCl_3$): δ7.65 (1H, *dd*, *J* = 5.4, 2.5 Hz, H-3), 6.16 (1H, *dd*, *J* = 5.4, 2.1 Hz, H-2), 2.93 (1H, *m*, H-4), 2.53 (1H, *dd*, *J* = 17.0, 6.7 Hz, H-5_a), 2.01 (1H, *dd*, *J* = 17.0, 2.2 Hz, H-5_b), 1.50-1.80 (2H, *m*, CH_2), 0.99 (3H, *t*, *J* = 6.6 Hz CH_3). δ_C (100 MHz; $CDCl_3$): 11.6 (CH_3), 27.0 (CH_2), 34.8 (C-4), 49.9 (C-5), 125.6 (C-2), 146.7 (C-3), 197.6 (CO).

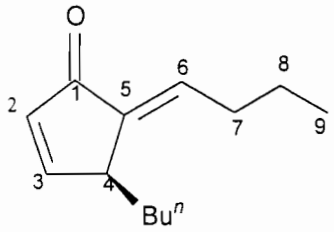
4-Butyl-5*E*-ethylidenecyclopent-2-enone (**74**):



A solution of **67** (150 mg, 0.65 mmol) and maleic anhydride (255 mg, 2.60 mmol) in 1,2-dichloroethane (7 mL) was treated with ethylaluminum dichloride (1 mL of a 1.0 M solution in hexane). The reaction was stirred for 1.5 h at 50^0C, cooled to ambient temperature and quenched with a saturated aqueous sodium hydrogen carbonate solution. The product was isolated by extraction with ether and the combined organic extract dried ($MgSO_4$) and concentrated

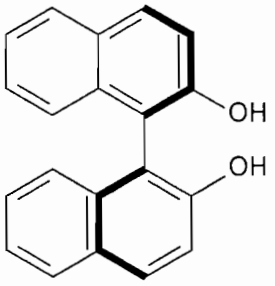
in *vacuo*. The residue was purified on silica-gel (10 g, EtOAc-hexane; 1:40) to give **74** (75 mg, 75 %) as a slightly yellow oil. IR: 1690 cm^{-1} (C=O). (Found: M^+, 164.1202. $C_{11}H_{16}O$ requires 164.1201). δ_H (300 MHz; $CDCl_3$): 7.53 (1H, *ddd*, *J* = 6.0, 2.7, 1.1 Hz, H-3), 6.61 (1H, *qt*, *J* = 7.3, 1.5, Hz, H-6), 6.30 (1H, *dd*, *J* = 6.0, 1.8 Hz, H-2), 3.51-3.42 (1H, *m*, H-4), 1.88 (3H, *d*, *J* = 7.3 Hz, =CH**CH_3**), 1.58-1.44 (1H, *m*), 1.39-1.19 (5H, *m*), 0.87 (3H, *t*, J = 6.96 Hz, **CH_3**). δ_C (75 MHz; $CDCl_3$): 13.8 (CH_3), 14.7 (CH_3), 22.8 (CH_2), 28.1 (CH_2), 31.8 (CH_2), 43.1 (C-4), 130.2 (C-5), 134.7 (C-2), 139.2 (C-6), 161.8 (3), 196.7 (CO).

4-Butyl-5-butylidene-cyclopent-2-enone (**75**):



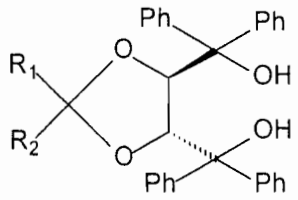
A solution of **68** (95 mg, 0.40 mmol) and maleic anhydride (98.1 mg, 1.00 mmol) in 1,2-dichloroethane (5 mL) was treated with ethylaluminum dichloride (0.7 mL of a 1.0 M solution in hexane). The reaction was stirred for 1.5 h at 50^0C, cooled to ambient temperature and quenched with a saturated aqueous sodium hydrogen carbonate solution. The product was isolated by extraction with ether and the combined organic extract dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified on silica-gel (5 g, EtOAc-hexane; 1:50) to give **75** (50 mg, 65%) as a slightly yellow oil. IR: 1670 cm^{-1}(C=O). (Found: M^+, 192.1509. $C_{13}H_{20}O$ requires 192.1514). δ_H (400 MHz; $CDCl_3$): 7.52 (1H, *ddd*, *J* = 6.0, 2.6, 0.9 Hz, H-3), 6.53 (1H, *t*, *J* = 7.7 Hz, H-6), 6.30 (1H, *dd*, *J* = 6.0, 2.0 Hz, H-2), 3.41-3.52 (1H, *m*, H-4), 2.31-2.12 (2H, *m*, $^{12}CH_2$), 1.87-1.22 (8H, *m*, 4xCH_2), 0.95 (3H, *t*, *J* = 7.3 Hz, CH_3), 0.87 (3H, *t*, *J* = 7.2 Hz, CH_3). δ_C (100 MHz; $CDCl_3$): 14.1 (CH_3), 14.1 (CH_3), 22.2 (CH_2), 23.0 (CH_2), 28.2 (CH_2), 31.3 (CH_2), 32.3 (CH_2), 43.5 (C-4), 134.9 (C-5), 135.6 (C-2), 138,3 (C-6), 162.1(C-3), 197.2 (CO).

Lewis-acid catalysed retro-Diels–Alder reactions in the presence of chiral ligand



(*R*)-(+)-BINOL

80



TADDOL

35a, R_1=R_2= Ph
35b, R_1=R_2= Me

1 mole equiv. Lewis-acid / chiral ligand 35a

Chiral ligand **35a** (0.42 g, 0.70 mmol) was dissolved in 1,2-dichloroethane (10 mL) and treated with ethylaluminum dichloride (0.70 mL of a 1 M solution in hexane) and the solution was stirred for 5 min at room temperature. A 1,2-dichloroethane solution of **51** (157 mg, 0.67 mmol) and maleic anhydride (0.2 g, 2.00 mmol) was then added gradually and the solution was stirred at 55^{0}C for 30 min. The reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous sodium hydrogen carbonate solution. The organic phase was isolated by extraction with ether and the combined extract dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified on silica-gel (30 g, EtOAc-Hexane; 1:20) and the unchanged starting material was recovered (83 mg, 55%). Unchanged starting material was reduced with diisobutylaluminum hydride to alcohol **77** which was subsequently esterified with Mosher's acid (Found: M^+, 442.1745. $C_{26}H_{25}F_3O_3$ requires 442.1756). The ^{19}F NMR *ee*-assay of the Mosher's ester of **77** gave a pair of ^{19}F NMR (-71.69 ppm and -71.98 ppm) singlets of equal integration values.

1 mole equiv. Lewis-acid / Chiral ligand 35a

Chiral ligand **35a** (0.18 g, 0.3 mmol) was dissolved in 1,2-dichloroethane (7 mL) and treated with ethylaluminum dichloride (0.3 mL of a 1M solution in

hexane) at 0^0C and the solution was stirred at 0 ^{0}C for 40 min (aging time). A 1,2- dichloroethane solution of **51** (67 mg, 0.30 mmol) and maleic anhydride (53 mg, 0.54 mmol) was then added gradually and the solution was stirred at room temperature for 50 min. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution and the product was isolated by extraction with ether. The combined organic extract was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified on silica-gel (15 g, EtOAc-Hexane; 1:20) and the unchanged starting material was recovered (36 mg, 60%). Unchanged starting material was reduced with diisobutylaluminum hydride to alcohol **77** which was subsequently esterified with Mosher's acid (Found: M^+, 442.1745. $C_{26}H_{25}F_3O_3$ requires 442.1756). The ^{19}F NMR *ee* assay of the Mosher's ester of **77** gave a pair of ^{19}F NMR: (-71.69 ppm and -71.98 ppm) singlets of equal integration values.

1.2 mole equiv. Lewis-acid / chiral ligand 35b

Chiral ligand **35b** (0.14 g, 0.30 mmol) was dissolved in dichloromethane and transferred to a suspension of powdered molecular sieves (0.3 g) in dichloromethane (7 mL). The mixture was treated with titanium tetrachloride (0.30 mL of a 1M solution in dichloromethane) and stirred for 1h at room temperature until a dark pink colour persisted. A solution of **50** (50 mg, 0.25 mmol) and maleic anhydride (75 mg, 0.75 mmol) in dichloromethane (2 mL) was then added gradually. The reaction mixture was stirred at room temperature for 3 h and quenched with a saturated aqueous sodium hydrogen carbonate solution. The organic phase was isolated by extraction with ether and the combined extract dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified on silica-gel (10 g, EtOAc-Hexane; 1:20) and the unchanged starting material was recovered (30 mg, 60 %). Unchanged starting material was reduced with diisobutylaluminum hydride to alcohol **76** which was subsequently esterified with Mosher's acid (Found: M^+, 422.2050. $C_{24}H_{29}F_3O_3$ requires 422.2070). The ^{19}F NMR *ee* assay of the Mosher's ester of **76** gave a pair of ^{19}F NMR (-70.29 ppm and -70.58 ppm) singlets of equal integration values.

1.1 mole equiv. Lewis-acid / chiral ligand 35b

Chiral ligand **35b** (0.14 mg, 0.30 mmol) was dissolved in dichloromethane (5 mL) and treated with ethylaluminum dichloride (0.3 mL, 0.30 mmol) at - 78^{0}C. The mixture was then consecutively stirred for 1 h at -78^{0}C and for 2 h at room temperature (aging period). The flask was cooled to -78^{0}C and a dichloromethane solution of **51** (60 mg, 0.27 mmol) was added gradually followed within 15 min by the maleic anhydride (52 mg, 0.54 mmol). The reaction mixture was stirred at room temperature for 15 h and quenched with a saturated aqueous sodium hydrogen carbonate solution. The organic phase was isolated by extraction with ether and the combined organic extract dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue purified on silica-gel (15 g, EtOAc-Hexane; 1:20) and unchanged starting material was recovered (44 mg, 73 %). Unchanged starting material was reduced with diisobutylaluminum hydride to alcohol **77** which was subsequently esterified with Mosher's acid (Found: M^+, 442.1745. $C_{26}H_{25}F_3O_3$ requires 442.1756). The ^{19}F NMR *ee* assay determination of the Mosher's ester of **77** gave a pair of ^{19}F NMR: (-71.69 ppm and -71.98 ppm) singlets of equal integration values.

0.1 mole equiv. Lewis-acid / chiral ligand 35b

Chiral ligand **35b** (25 mg, 0.05 mmol) was dissolved in dichloromethane (3 mL) and treated with ethylaluminum dichloride (0.05 mL, 1M solution in hexane) at - 78^{0}C. The solution was then stirred at room temperature for 2.5 h, cooled again to - 78^{0}C and a dichloromethane solution of **51** (113 mg, 0.50 mmol) was added gradually. The maleic anhydride (61 mg, 0.62 mmol) was added after 20 min. The reaction mixture was warmed slowly to room temperature and stirred for 17 h. On TLC analysis, there was no evidence of the formation of a product.

1 mole equiv. Lewis-acid / chiral ligand 35b

Chiral ligand **35b** (140 mg, 0.30 mmol) was dissolved in toluene (5 mL) and stirred with dimethylaluminum chloride (0.30 mL, 0.30 mmol) at - 78^{0}C for 20 min. The flask was warmed slowly to room temperature and stirred for 40 min. The mixture was then cooled to 0^{0}C and a toluene solution of **51** (70 mg, 0.30 mmol) was added. The reaction mixture was stirred for 20 min before the addition of maleic anhydride (32 mg, 0.32 mmol) and stirred for 2 h at 50^{0}C. The flask was brought to ambient temperature and quenched with a saturated aqueous sodium hydrogen carbonate solution. The product was isolated by extraction with ether, the combined organic extract dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified on silica-gel (20 g, EtOAc-Hexane; 1:20) and the unchanged starting material was recovered (30 mg, 43 %). Unchanged starting material was reduced with diisobutylaluminum hydride to alcohol **77** which was subsequently esterified with Mosher's acid (Found: M^+, 442.1745. $C_{26}H_{25}F_3O_3$ requires 442.1756). The ^{19}F NMR *ee* assay of the Mosher's ester of **77** gave a pair of ^{19}F NMR: (-71.69 ppm and -71.98 ppm) singlets of equal integration values.

1.5 mole equiv. Lewis-acid / chiral ligand 35b

Chiral ligand **35b** (0.15 g, 0.30 mmol) was dissolved in dry toluene (8 mL) containing molecular sieves (1.5 g) and treated with dichlorotitanium diisopropoxide (0.30 mL, 0.30 mmol) at 0^{0}C. The mixture was stirred at 0^{0}C for 1 h and a solution of **51** (43.5 mg, 0.2 mmol) and maleic anhydride (88 mg, 0.90 mmol) in dry dichloromethane (8 mL) was added gradually. The reaction mixture was stirred for 15 h at 0-55^{0}C. On TLC analysis, there was no evidence of the formation of a product.

0.3 mole equiv. Lewis-acid / BINOL (78)

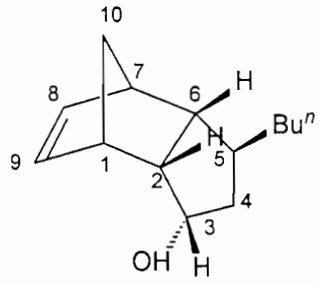
BINOL (30 mg, 0.10 mmol) was dissolved in dichloromethane (4 mL) and stirred with dimethylaluminum chloride (0.1 mL, 0.1 mmol) at room temperature for 50 min. A dichloromethane solution of **51** (70 mg, 0.31 mmol) and maleic anhydride (31 mg. 0.31 mmol) was added gradually and the progress of the reaction followed by TLC. After a 30 min room temperature and 2 h, 40^0C stirring, the reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous sodium hydrogen carbonate solution. The product was isolated by extraction with ether and the combined organic extracts dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified on silica-gel (20 g, EtOAc-Hexane; 1:20) and unchanged starting material was recovered (50 mg, 70 %). Unchanged starting material was reduced with diisobutylaluminum hydride to alcohol **77** which was subsequently esterified with Mosher's acid (Found: M^+, 442.1745. $C_{26}H_{25}F_3O_3$ requires 442.1756). The ^{19}F *ee* assay of the Mosher's ester of **77** gave a pair of ^{19}F NMR: (-71.69 ppm and -71.98 ppm) singlets of equal integration values.

0.5 mole equiv. Lewis acid / BINOL (80)

BINOL (57.5 mg, 0.20 mmol) was dissolved in 1,2-dichloroethane (5 mL) and stirred with dimethylaluminum chloride (0.20 mL, 0.20 mmol) at 25^0C for 50 min. A dichloromethane solution of **51** (90 mg, 0.40 mmol) and maleic anhydride (31 mg. 0.31 mmol) was added and the mixture was stirred for 1h. The temperature was raised to 50^0C and after a 1 h stirring the reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous sodium hydrogen carbonate solution. The product was isolated by extraction with ether, the combined organic extract dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified on silica-gel (20 g, EtOAc-Hexane; 1:20) and the unchanged starting material was recovered (38.5 mg, 55%). Unchanged starting material was reduced with diisobutylaluminum hydride to alcohol **77** which was subsequently

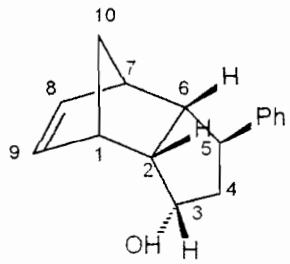
esterified with Mosher's acid (Found: M^+, 442.1745. $C_{26}H_{25}F_3O_3$ requires 442.1756). The ^{19}F *ee* assay of the Mosher's ester of **77** gave a pair of ^{19}F NMR (-71.69 ppm and -71.98 ppm) singlets of equal integration values.

***Exo*-5-*n*-Butyl-*endo*-3-hydroxytricyclo-[5.2.1.0^{2,6}]-dec-8-en-3-ol (76)**:



A solution of **50** (40 mg, 0.20 mmol) in toluene (2 ml) was placed in an ice bath (0^{0}C) and treated with diisobutylaluminum hydride (0.40 mL of 1M solution in toluene). The reaction mixture was stirred for 2 h at 0^{0}C and after this period, a 1:1 toluene-methanol solution (3 ml) was added slowly with cooling, followed by 2.0 mL of hydrochloric acid (2 M) solution. After 30 min stirring, the solid aluminium salts were filtered and the organic layer separated. The aqueous layer was extracted with ether (2 x 10 mL) and the combined organic layers dried ($MgSO_4$), and the solvent evaporated under reduced pressure and concentrated in *vacuo*. The residue was chromatographed on silica-gel (5 g, EtOAc-hexane; 1:20) to give the alcohol **76** as a colourless crystalline solid (31.4 mg, 76%). m.p.: 62-63^{0}C (from hexane). (Found: M^+, 206.1665. $C_{14}H_{22}O$ requires 206.1670). δ_H (300 MHz; $CDCl_3$): 6.37 (1H, *dd*, *J* = 5.5, 3.0 Hz, H-8 or H-9), 6.12 (1H, *dd*, *J* = 5.5, 3.2 Hz, H-8 or H-9), 4.24 (1H, *dd*, *J* = 6.2, 5.1 Hz, H-3), 2.90-2.86 (1H, *m*, H-1), 2.84-2.76 (2H, *m*, H-7 and H-2), 2.36-2.29 (1H, *dd*, *J* = 4.7, 4.3 Hz, H-6), 1.76-1.69 (1H, *m*, H-4$_{endo}$), 1.65 (1H, *s*, OH), 1.58-1.50 (2H, *m*, H-10$_a$ or H-10$_b$ and H-4$_{exo}$), 1.44 (1H, *d*, *J* = 7.9 Hz, H-10$_a$ or H-10$_b$), 1.43-1.40 (1H, *m*, H-5),1.38-1.22 (6H, m, (**CH$_2$**)$_3$) 0.89 (3H, *t*, *J* = 6.8 Hz, **CH$_3$**). δ_C (75 MHz; $CDCl_3$): 13.9 (CH_3), 22.8 (CH_2), 30.5 (CH_2), 35.9 (CH_2), 38.9 (CH), 44.9 (CH), 45.3 (CH), 45.7 (CH_2), 53.2 (C-10), 54.1 (C-7), 54.2 (C-1), 73.4 (C-3), 134.9 (C-8 or C-9), 137.1(C-8 or C-9).

***Exo*-5-Phenyl-*endo*-3-hydroxytricyclo-[5.2.1.0^{2,6}]-dec-8-en-3-ol (77)**:



A solution of **51** (67.3 mg, 0.30 mmol) in toluene (4 ml) was placed in an ice bath (0^{0}C) and treated with diisobutylaluminum hydride (0.60 mL of 1M solution in toluene). The reaction mixture was stirred for 2 h at 0^{0}C and after this period, a 1:1 toluene-methanol solution (5 ml) was added slowly with cooling, followed by 2.0 mL of hydrochloric acid (2 M) solution. After 30 min stirring, the solid aluminium salts were filtered and the organic layer separated. The aqueous layer was extracted with ether (2 x 15 mL) and the combined organic layers dried ($MgSO_4$), and the solvent evaporated under reduced pressure and concentrated in *vacuo*. The residue was chromatographed on silica-gel (10 g, EtOAc-hexane; 1:20) to give the alcohol **77** as a colourless crystalline solid (53.6 mg, 79%). m.p.: 64-65^{0}C (from hexane). (Found: M^+, 224.1511. $C_{16}H_{18}O$ requires 226.1201). δ_H (300 MHz; $CDCl_3$): 7.15-7.38 (5H, m, aromatic), 6.61 (1H, *dd*, *J* = 5.4, 3.1 Hz, H-8 or H-9), 6.41 (1H, *dd*, *J* = 5.4, 3.2 Hz, H-8 or H-9), 4.64 (1H, *dd*, *J* = 6.2, 5.0 Hz, H-3), 2.94-2.87 (1H, *m*, H-1), 2.87-2.79 (2H, *m*, H-7 and H-2), 2.40-2.30 (1H, *dd*, *J* = 4.6, 4.2 Hz, H-6), 2.22 (1H, *m*, H-5), 2.10-1.90 (1H, m, H-4_{endo}), 1.58-1.50 (2H, m, H-10_a or H-10_b and H-4_{exo}), 1.44 (1H, *d*, *J* = 7.9 Hz, H-10_a or H-10_b). δ_C (75 MHz; $CDCl_3$): 42.9 (CH), 46.9 (CH), 50.0 (CH), 52.3 (C-10), 53.2 (C-5), 54.1 (CH), 54.2 (CH), 73.4 (C-3),126.2 (C-ar.), 126.6 (2xC-ar.), 128.7 (2xC ar.), 134.9 (C-8 or C-9), 136.7(C-8 or C-9), 146.8 (C-ar.).

References:

1. A. Rossi, G. Elia and M. G. Santoro, *J. Biol. Chem.*, **1996**, *271*(50), 32192-32196.
2. R. I. Morimoto, K. D Sarge and K. Abravaya, *J. Bio. Chem.*, **1992**, *267*, 21987-90.
3. R. Mestril, S. Chi, M.R. Sayen, K. O'Reilly and W. H. Dillman, *J. Clin. Invest.* **1994**, *93*, 759-67.
4. A. Rossi. G. Elia and M. G. Santoro, *Proc Natl. Acad. Sci. USA*, **1997**, *94*, 746-50.
5. C. Rozera, A. Carattoli, A. De Marco, C. Amici, C. Giorgi and M. G. Santoro, *J. Clin. Invest.* **1996**, *97*, 1795-803.
6. A.S. Baldwin, *Annu. Rev. Immunol.* **1996**, *14*, 649-81.
7. R. Antonio, P. Kapahi, G. Natoll, T. Takahashi, Yi Chen, M. Karin and M. G. Santoro, *Nature*, **2000**, *403*, 103-109.
8. M. G. Santoro, *Experientia*, **1994**, *50*, 1039-1047.
9. G. Nabel and D. Baltimore, *Nature*, **1987**, *326*, 711-3.
10. F. Bureau, C. Desmet, D. Meltte, F. Jaspar, C. Volanti, A. Vanderplasschen, P. Pastoret, J. Piette and P. Lekeux, *The J. of Immunol.*, **2002**, *168*, 5318-5325.
11. S. Narumiya, Y. Sugimoto and F. Ushikubi, *Physiological. Rev.*, **1999**, *79*(4), 1193-1226.
12. T. G. Brock, R. W. McNish and M. P. Golden, *J. of Bio. Chem.*, **1999**, *274*(17), 11660-11666.
13. N. A. Nelson, *J. of Med. Chem.*, **1974**, *17*(9), 911-918.
14. S. Roberts, G. Santoro and E. Sickle, *Chemistry in Britain*, **2001**, *May* 34-36.
15. M. Suzuki, Y. Morita, H. Koyano, M. Koga and R. Noyori, *Tetrahedron*, **1990**, *46*(13/14), 4809-4822.
16. M. Suzuki, M. Mori, T. Niwa, R. Hirata, K. Furuta, T. Ishikawa and R. Noyori, *J. Am. Chem. Soc*, **1997**, *119*, 2376-2385.
17. G. Zanoni, F. Castronovo, E. Perani and G. Vidari, *J. Org. Chem.* **2003**, *68*, 6803-6805.

18. M. A. Tius, J. Busch-Petersen and M. Yamashita, *Tetrahedron Letters*, **1998**, *39*, 4219-4222.
19. M. E. Krafft and C. Wright, *Tetrahedron Letters*, **1992**, *33*(2), 151-152.
20. S. M. Roberts, M. G. Santoro and E. S. Sickle, *J. Chem. Soc., Perkin Trans. I*, **2002**, 15, 1735-1742.
21. T. Morimoto, T. M. Hirano and X. Zhung, *J. Chem. Soc. Perkin Trans. II* **1988**, 909-912.
22. J. R. Gilmore and J. M. Mellor, *J. Chem. Soc. (C)*, **1971**, 2355-2357.
23. A. S. Demir, O. Reis and A. C. Igdir, *Tetrahedron*, **2004**, *60*, 3427-3432.
24. S. Takano, M. Moriya, K. Tanaka and K. Ogasawara, *Synthesis*, **1993**, 687-688.
25. K. Tanaka and K. Ogasawara, *Synthesis*, **1995**, 1237-1239.
26. T. Ito, Y. Okamoto, T. Matsumoto, *Bull. Chem. Soc. Jpn.*, **1985**, 3631-3632.
27. S. Easwar, B. Shrivallabh, B. Desai, N. P. Argade and K. N. Ganesh, *Tetrahedron Asymmetry*, **2002**, *13*, 1367-1371.
28. K. Ogasawara, *Pure and Appl. Chem.*, **1994**, *66*(10/11), 2119-2122.
29. G. Piancatelli, A. Scettri and M. D'Auria, *Synthesis*, **1982**, 245-248.
30. Y. Cheng, W. Liu and S. Chen, *Synthesis*, **1980**, 223-224.
31. D. H. Williams and I. Fleming, *Spectroscopic Methods in Organic Chemistry*, McGraw-Hill, Berkshire, **1997**, *Fifth Edition*.
32. B. H. Lipshutz, R. S. Wilhelm and J. A. Kozlowski, *J. Org. Chem.*, **1984**, *49*(21), 3938-3942.
33. P. M. A. Dols, M. M. H. Verstappen, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **1993**, *49*(48), 11353-11372.
34. J. Zhu, J. vander Hoeven, J. Slief, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **1995**, *51*(40), 10953-10968.
35. M. Isobe, S. Kondo, N. Nagasawa and T. Goto, *Chemistry Letters*, **1977**, 679-682.
36. A. J. H. klunder, W. B. Huizinga, A. J. M. Hulshof and B. Zwanenburg, *Tetrahedron Letters*, **1986**, *27*(22), 2543-2546.
37. A. J. H. klunder, W. B. Huizinga, P. J. M. Sessink and B. Zwanenburg, *Tetrahedron Letters*, **1987**, *28*(3), 357-360.

38. B. J. Childs and G. L. Edwards, *Tetrahedron Letters*, **1993**, *34*(33), 5341-5342.
39. P. A. Grieco and N. Abood, *J. Chem. Soc., Chem. Commun.*, **1990**, 410-412.
40. A. P. Marchand and V. Vidyasagar, *J. Org. Chem.*, **1988**, *53*, 4412-4414.
41. A. Ichihara, *Synthesis Review*, **1987**, 207-222.
42. P. A. Grieco and N, Abood, *J. Org. Chem.*, **1989**, *54*, 6008-6010.
43. C. G. Krespan, *Chemical Reviews*, **1996**, *96*(8), 3271-3273.
44. H. O. House, M. Gall and H. D. Olmstead, *J. Org. Chem.*, **1971**, *36*(16), 2361-2371.
45. L. Xie, K. M. Isenberger, G. Held and L. M. Dahl, *J. Org. Chem.*, **1997**, *62*, 7516-7519.
46. H. Y. Wu, K. A. M. Walker and J. T. Nelson, *J. Org. Chem.*, **1999**, *55*, 5074-5078.
47. J. d'Angelo, *Tetrahedron*, **1976**, *32*, 2979-2990.
48. F. Naf and R. Decorzant, *Helvetica Chimica Acta*, **1974**, *57*, 1317-1327.
49. M. Iqbal and P. Evans, *Tetrahedron letters*, **2003**, *44*, 5741-5745.
50. G. Mehta and J. D. Umarye, *Organic Letters*, **2002**, *4*(7) 1063-1066.
51. K. Takasu, S. Mizutani, M. Noguchi, K. Makita and M. Ihara, *Organic Letters*, **1999**, *1*(3), 391-393
52. K. K. Heng and R. A. J. Smith, *Tetrahedron*, **1979**, *35*, 425-435.
53. A. J. H. Klunder, J. Zhu and B. Zwanenburg*, *Chem. Rev.* **1999**, *99*, 1163-1190.
54. M. Suzuki, A. Yanagisawa and R. Noyori, *J. Am. Chem. Soc.*, **1988**, *110*(14), 4718-4726.
55. P. J. Garratt and S. B. Neoh, *J. Amer. Chem. Soc.*, **1975**, 3257-3258.
56. a) R. K. Sharma and J. L. Fry, *J. Org. Chem.*, **1983**, *48*(12), 2113-2114. b) W. Yu and Z. Jin, *Tetrahedron Letters*, **2001**, *42*, 369-372.
57. E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **1972**, *94*, 6190.
58. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn and J. Lampe, *J. Org. Chem.*, **1980**, *45*, 1066-1081.

59. I. Kuwajima, E. Nakamura and M. Shimuzu, *J. Amer. Chem. Soc.*, **1982**, *104*, 1025-1030.
60. P. Brownbridge, *Synthesis*, **1983**, 1-28.
61. J. Wiel and F. Rouessac, *J. Chem. Soc. Chem. Comm.*, **1976**, 446-447.
62. U. Pindur, G. Lutz and C. Otto, *Chem. Rev.* **1993**, *93*, 741-761.
63. S. Yamabe andT. Minato, *J. Org. Chem.*, 2000, *65*, 1830-1841.
64. V. Branchadel, A. Oliva and J. Bertram, *Chemical Physics Letters*, **1985**, *113*(2), 197-201.
65. B. Henri. Kagan and O. Riant, *Chem. Rev.* **1992**, *92*, 1007-1019.
66. S. Wallbaum and J. Martens, *Tet. Asymm.*, **1992**, *3*(12), 1475-1504.
67. K. Narasaka, *Synthesis*, **1991**, 1-5.
68. *Stereo Controlled Organic Synthesis*, B.M. Trost, Ed., IUPAC Secretariat, Oxford, *1994*.
69. Clayden, Green, Warren and Wothers, *Organic Chemistry*, **2001**.
70. D. Parker, *Chem. Rev.* **1991**, 1441-1457.
71. V. Emilio, U. Costa and M. Axt, *Magnetic Resonance in Chemistry*, **1996**, *34*, 929-931.
72. D. E. Ward and C. K. Rhee, *Tetrahedron Letters*, **1991**, *32*(49), 7165-7166.
73. J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **1971**, 641-645.
74. R. D. Little and K. D. Moeller, *J. Org. Chem.*, **1983**, *48*, 4487.
75. J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.* **1969**, *34*(9), 2543-2549.
76. D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals,* Pergammon, Oxford, **1988**, third edition
77. M. Casey, J. Leonard, B. Lygo and G. Procter, Advanced *Practical Organic Chemistry*, Blackie, Glasgow and London, **1990**, first edition